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CORONARY HEART DISEASE AND PHYSICAL ACTIVITY OF WORK

EVIDENCE OF A NATIONAL NECROPSY SURVEY*

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It has previously been shown that the drivers of London's double-decker buses are more likely to die suddenly from "coronary thrombosis" than the conductors, and that Government clerks suffer more often from rapidly fatal cardiac infarction than do postmen.[43] On the basis of these and similar observations a hypothesis has been stated that *men in physically active jobs have a lower incidence of coronary (ischaemic) heart disease in middle-age than men in physically inactive jobs. More important, the disease is not so severe in physically active workers, tending to present in them in relatively benign forms.*

It is a principle of epidemiological research of this type to seek evidence from as many, as various, and as independent sources as possible.[40] The present report deals with the frequency, in relation to occupation, of ischaemic myocardial fibrosis in men dying from causes other than coronary heart disease itself. These myocardial scars are often evidence of early coronary heart disease and of less severe, or at any rate non-lethal, ischaemia. Thus the present study provides a picture of coronary heart disease in one of its simpler forms, and this may help in elucidating social connexions. At the same time another test of the hypothesis is made, using quite different data from the previous inquiries and upon quite another aspect of the condition. The inquiry it was hoped would provide some information on the pathological mechanisms of any differences with physical activity of work that were found; and in particular we sought to learn something about the relationships of occupation to coronary artery disease. In brief, Can the hearts of men be seen to vary with the kind of work they have done? At what phases in the complex of coronary-myocardial disease as a whole can this particular "cause"—physical activity/inactivity—be seen to operate? More generally the inquiry was intended to provide a statistical account of the coronary arteries of the middle-aged British male population, 1954–6.[42]

Method

Through the universities and regional hospital boards we appealed personally to all pathologists in the National Health Service who might regularly be in charge of post-mortem examinations to co-operate in the inquiry, and the pathologists of 206 hospitals or hospital groups—between 85% and 90% of the "possibles"—very kindly agreed. We cannot be more precise about this fraction, because it is not known whether some of those who did not reply at all to our letters were in fact regularly responsible for appreciable numbers of necropsies.

Each pathologist was invited to provide particulars on a standard form of 25 consecutive unselected necropsies on men aged 45–70 years, no matter what the cause of death or how the case came to necropsy. 5,000 reports were sent to us: trial runs with records from 1944 to 1951 in the Pathological Institute of the London Hospital[39 60] had encouraged the hope that with such numbers stable group patterns would emerge. In all cases *macroscopic details* were requested of *disease in the coronary arteries*, its nature, amount, and distribution, with descriptions of any stenosis; and of *fibrosis of the myocardium of the left ventricle* and *interventricular septum*, using lesions of 1 cm. in any dimension as markers; and the *heart weight*. Particulars were also asked about the main causes of death and other important clinical and pathological findings such as valvular heart disease, including especially aortic stenosis. By appealing for detailed descriptions of lesions seen, discouraging evaluations such as "slight" or "much," and giving guidance on terminology if not on technique, we hoped to reduce the variability of such procedures. It was postulated, moreover, that the variability in observation and recording over so many departments of pathology would be "random" in relation to the main factor with which pathology was to be correlated—physical activity of work.

The pathological data on each record relating to disease in the coronary arteries and fibrosis of the myocardium were graded, agreed, and coded by at least two and often three physicians in the unit. It took many months to define appropriate scales; but finally scales emerged that made pathological sense, were simple in use, having no more than five points, and the gradings on which proved highly reproducible by ourselves and by others.

Pathologists were also invited to give details of the *last occupation* of the deceased, but in many cases this information had to be obtained by the unit from the

*Part of this report was included in the Ernestine Henry Lecture delivered by one of us (J. N. M.) before the Royal College of Physicians of London on June 10, 1958.

General Register Office. The last stated occupation, apart from other difficulties,[57] is unlikely to be an exact indicator of men's jobs during their middle-age. The present inquiry, however, is concerned only with *type of job* in terms of its characteristic *physical activity*. Some special categories apart, the last job is probably by and large an adequate indicator of this. (Occupational histories of their national series kindly made available to us by Doll and Hill[14 15] showed on analysis that among 152 fatal cases of lung cancer in men aged 55–64, 80% had been in the same job for more than their last 10 years and a further 10% had changed jobs during the last 10 years of life but remained in the same physical activity category. These proportions over 15 years were 70% and 14% respectively; over 20 years, 61% and 17%.)

The 1,700 different descriptions of occupations included in the 5,000 returns of the present inquiry were classified, in terms of the physical activity habitually involved, by two experts in industrial medicine who first graded all the jobs independently and then presented the unit with an agreed coding. They used a three-point scale: typically "light" jobs (for example, schoolmaster, bus-driver, clerk of any description); "active" jobs (for example, postman, carpenter); or "heavy" jobs (for example, boilermaker, dock labourer). Light jobs, that is, include sedentary; heavy include the heaviest.

The technical problems involved in such studies as the present have already been considered,[37 40 42] and further comments are included in this and will be given in subsequent papers. There are many imperfections in the data on both biological and social sides of the equations to be attempted. The method used, like any other, and more than most, has its limitations as well as its possibilities. In particular, detailed occupational histories could not be obtained, which may be a considerable loss, and more than occupation-wise, since related economic/nutritional standards varied far more widely in the 1930s than in the 1950s.[13 36 51] Moreover, considered agreement on pathological techniques, not to say uniformity, has been sacrificed for numbers. The crucial issue was that of range of occupation: only a countrywide and comprehensive survey gathering large numbers of cases from many different centres could include enough men in the diminishing categories of truly "heavy" workers—coal hewers, farm labourers, men in heavy engineering, and the like. The interest of the questions that can be asked only from the present kind of study will, it is hoped, compensate for what has had to be forgone—and suggest what might next be done.[42]

Material

Necropsy material may be classified for our present purposes as follows[39 42]:

Group A.—Deaths due to coronary heart disease: coronary heart disease itself; or with hypertension, and/or other pathology; and including slow, congestive cardiac failure as well as the more numerous sudden deaths. There were about 1,200 altogether in Group A.

Group B.—Deaths from conditions associated with a specially high prevalence or severity of coronary artery disease—for example, deaths from hypertension and its complications; deaths from vascular disease in sites other than the coronary arteries, with or without hypertension; ("senile") aortic stenosis; deaths from destructive renal disease; the cases of diabetes. In addition to such well-recognized associations it was noticed that deaths from peptic ulcer in the present material showed a significant excess of occlusive coronary artery disease, and these deaths were therefore included in Group B. This group of 1,000 cases was called the *high coronary artery disease group.*

Group C.—Deaths from other conditions, the remainder and majority of necropsies, including injuries, infections, cancers. No disease or disease-group with 100 cases or over included in Group C showed significantly more or significantly less coronary artery disease at the 5% level than the remainder, as judged by the prevalence and amount of mural disease and the frequency of lumen narrowing of 50% or more in a major artery. This group is therefore called the *basal group* as regards coronary artery disease. There were 2,800 cases in it.

The present report deals with the 3,800 cases in Groups B and C. Brief reference is also made to Group A, but these cases will be fully considered on another occasion.

Ischaemic Myocardial Fibrosis

In some 500 of the 3,800 non-coronary deaths fibrosis was reported in the myocardium of the left ventricle and/or septum. All these records were scrutinized, and any subjects with rheumatic heart disease or other possible cause of myocardial fibrosis, the collagen-vascular diseases, for example, or ostial syphilis, were excluded; cases with generalized, "diffuse" fibrosis not otherwise described were also discarded. ("Myocarditis" was rarely mentioned by the pathologists; no microscopical examination was requested.) This left close on 400 cases with scars, commonly in the lower, antero-lateral walls of the left ventricle, in the front of the septum, or high on the posterior wall, which are presumptively ischaemic, will henceforth be regarded as *ischaemic myocardial fibrosis,* and have alone been analysed. In most of these 400 cases there was much coronary artery disease and a report of topical coronary narrowing.* The few scars in the right ventricle were ignored.

Scars were classified on two axes, whether they were single or multiple and large or small. Two main types of ischaemic myocardial fibrosis soon identified themselves, and provided a quick first answer to one of the main questions of the inquiry:

Type 1.—The *large, discrete patch* of fibrosis, over 1.5 cm. in one dimension, and often solitary. These patches were commonly transmural, and they are presumably the healed end-result of major and maybe acute infarction—"large healed infarcts"—or sometimes of confluent lesser infarcts. They were usually associated with occlusion or near-occlusion in the related main coronary artery, often high in it, rather than with lesser coronary narrowing. All aneurysmal dilatations have been included here, and also some large areas of fibrosis which were not clearly circumscribed.

Type 2.—Small, multiple scars, in the left ventricular wall, the septum, or papillary muscles which were usually thinner and less defined than type 1 and were associated in this material mostly with minor degrees of focal narrowing, low in a main coronary artery, for example, or in smaller branches. These scars are commonly regarded as the product of lesser and more slowly developing coronary insufficiency and myocardial ischaemia. However, some of this "focal myocardial fibrosis"[21] may well be the result of very small infarcts.

It was soon apparent that the occurrence of a large patch was strongly related to physical activity/inactivity of occupation, the occurrence of the small multiple scars less so. Discrete patches of 0.5–1.5 cm. in diameter, and some very small scars also regarded as ischaemic, were all found to behave much more like type 2 in relation to occupation, to coronary narrowing (and, as seen later, to hypertension)

*In the minority of scars in which there was no record of topical coronary narrowing the same relationships with physical activity of occupation were observed as among the majority with a record of obstructive arterial disease. Only one tabulation is therefore presented.

than the large healed infarcts of type 1, and they have therefore been classified to type 2. All type 2 scars will, for convenience, be called "focal myocardial fibrosis." Mixed cases with both types of fibrosis were included with type 1.[1 21 47 63 69]

Results

As stated, this report deals mainly with the (presumptively) ischaemic myocardial fibrosis found in a national sample of 3,800 non-coronary deaths in middle-aged men. Table I sets out the findings, first for the 2,800 miscellaneous deaths from injuries, infections, cancers, etc., and, below, for the 1,000 deaths from hypertensive and other vascular disorders, the deaths in diabetics, etc. Throughout, in each line of Table I, the rate among the "light" workers (e.g., *2.0*% in the first line) is substantially higher than in the "heavy" (*0.3*% in the first line). The "active" rates mostly fall between, but occasionally are below the "heavy" (as in the second line of the Table). This trend was repeated time after time in the analysis of Group C, Group B, and various pathological, medical, and social subdivisions of these; it was found in Scotland, Wales, Greater London, and the rest of England, separately; in London teaching hospitals, other teaching hospitals, and non-teaching hospitals when these were distinguished; and it was also the main finding of the trial study of the 1944–51 Woods and Russell London Hospital cases.

The results in Table I can be summarized thus:

1. Disregarding age, cause of death category, and type of scarring (last line of the Table) there is twice as much ischaemic myocardial fibrosis in the "light" workers as in the "heavy"—*13.4*% compared with *6.8*%.

2. There is a stronger gradient with physical activity of occupation in the cases with large fibrous patches—threefold overall, *3.5*% to *1.2*%—than in those with the smaller/multiple scars—*9.9*% to *5.7*% (second and third last lines of Table I).

3. This excess of large healed infarcts among the "light" workers is more evident in the younger age group than at 60–70 years. At 45<60 years, in Groups B and C combined, there are four to five times as many of these scars in "light" workers as in "heavy"; at 60–70, two to three times as many (Table II).

Numbers are often small, but it seemed preferable to set out all the data instead of amalgamating the active and heavy ocupations and comparing these with the light, which was the alternative the data indicated. Table I emphasizes that even among the heavy occupations there is a good deal of ischaemic myocardial fibrosis; though, in fact, large healed infarcts were as common in light workers aged 45–54 (2.0%) as in heavy aged 65–70 (1.9%).

TABLE II.—*Large Healed Myocardial Infarcts.* 3,800 *Non-coronary Deaths. Men*

Ages	Occupation		
	Light	Active	Heavy
45<60	*2·3%*	*1·3%*	*(0·49%)*
60–70	*4·7%*	*2·6%*	*1·8%*

TABLE I.—*Proportions with Ischaemic Myocardial Fibrosis by Physical Activity of Occupation ("Light," "Active," "Heavy").* 3,800 *Non-coronary Deaths. Males Aged* 45–70

Age	Ischaemic Myocardial Fibrosis	Occupation					
		Light		Active		Heavy	
	Deaths from Conditions in "Basal" Group						
45<60	No. of cases	509		516		324	
	With large fibrous patch	10		5		1	
	Rate %		*2·0%*		*1·0%*		*(0·3%)*
	With smaller multiple scars	21		14		9	
	Rate %		*4·1%*		*2·7%*		*2·8%*
60–70	No. of cases	486		518		344	
	With large fibrous patch	16		12		3	
	Rate %		*3·3%*		*2·3%*		*(0·9%)*
	With smaller multiple scars	45		34		19	
	Rate %		*9·3%*		*6·6%*		*5·5%*
45–70	No. of cases	995		1,034		668	
	Total with ischaemic myocardial fibrosis	92		65		32	
	Rate %		*9·2%*		*6·3%*		*4·8%*
	Deaths from Conditions in "High" Coronary Artery Disease Group						
45<60	No. of cases	193		189		82	
	With large fibrous patch	6		4		1	
	Rate %		*3·1%*		*(2·1%)*		*(1·2%)*
	With smaller multiple scars	33		16		5	
	Rate %		*17·1%*		*8·5%*		*6·1%*
60–70	No. of cases	252		206		112	
	With large fibrous patch	19		7		5	
	Rate %		*7·5%*		*3·4%*		*4·5%*
	With smaller multiple scars	43		32		16	
	Rate %		*17·1%*		*15·5%*		*14·3%*
45–70	No. of cases	445		395		194	
	Total with ischaemic myocardial fibrosis	101		59		27	
	Rate %		*22·7%*		*14·9%*		*13·9%*
	All Non-coronary Deaths						
45–70	No. of cases	1,440		1,429		862	
	With large fibrous patch	51		28		10	
	Rate %		*3·5%*		*2·0%*		*1·2%*
	With smaller multiple scars	142		96		49	
	Rate %		*9·9%*		*6·7%*		*5·7%*
	Total with ischaemic myocardial fibrosis	193		124		59	
	Rate %		*13·4%*		*8·7%*		*6·8%*

National Necropsy Survey, Scotland, England and Wales, 1954–6. Data from 206 hospitals or hospital groups.

The number of non-coronary deaths that were analysed varied slightly around 3,800, depending on the availability of data.

Forty-six cases have been omitted from this and all subsequent tables because information was inadequate, or it was impossible to classify a main cause of death to Groups A, B, or C (e.g., 12 cases of polyarteritis nodosa). In addition 114 non-coronary deaths have been omitted from tables dealing with the physical activity of occupation because the last job was unknown or could not be classified.

Occupations were classified by Dr. R. Murray and Dr. D. Turner.

Throughout these tables rates of ischaemic myocardial fibrosis are printed in italic. Rates based on a numerator of less than 5 cases are bracketed ( ).

45<60 years = 45–59 incl. 60–70 years = 60–70 incl. 45–70 years = 45–70 incl.

Because of the similarity of age distributions crude rates have been used throughout the analysis and tables in amalgamations of 45–70 years inclusive.

Tests of Significance.—The test used in this table (and throughout this paper where relevant) is the test for linear trends in proportions (P. Armitage, *Biometrics*, 1955, **11**, 375). A significant value of p indicates that the trend in the proportions (percentages) from "light" through "active" to "heavy" occupations is unlikely to be due to chance. The p values in separate subgroups—e.g., age groups 45<60 and 60–70—have usually been combined in the total groups—e.g., aged 45–70—the method of combination allowing for the fact that the trend was in the same direction in each subgroup.

Third last line, $p<0{\cdot}001$; 2nd last line, $p<0{\cdot}001$; last line, $p<0{\cdot}001$.

Hypertension

Pathologists were asked to report any clinical or pathological evidence of hypertension, and much detailed information was provided for us. Using one at least of these criteria—(*a*) a clinical history of hypertension with record of diastolic pressure over 110; often there were particulars of treatment; (*b*) "concentric" left ventricular hypertrophy; or (*c*) in younger cases particularly, left ventricular hypertrophy not otherwise described or explained, together with nephrosclerosis—it was possible to distinguish those with "record or evidence of hypertension" from the "others." Close on 10% of the "basal" Group C had incidental hypertension as so defined. In almost half the cases of the "high coronary artery disease" Group B hypertension was present, and considered usually to be a principal factor in the death—for example, in many of the deaths from cerebrovascular disease.

The prevalence of ischaemic myocardial fibrosis in relation to hypertension is summarized in Table III, which shows no difference in the large fibrous patches (large healed infarcts) but substantially more of the smaller/multiple scars (focal myocardial fibrosis) among the hypertensive ($p<0.001$). This latter excess, it may be noted, held for each of the subtypes of small scars and multiple scars included in type 2; whence the use of the term "focal myocardial fibrosis" for all of type 2 scars.

Table IV continues this analysis by occupation, and includes all the cases in Groups B and C—that is, all the non-coronary deaths. There is nothing of interest in the large fibrous patches, both the hypertensive (e.g., 4th line, in italics, left half of the table) and the "others" (e.g., first line in italics, right half of the table) showing the expected

TABLE III.—*Proportions With Ischaemic Myocardial Fibrosis. Factor of Hypertension. 3,800 Non-coronary Deaths. Males Aged 45–70*

Ischaemic Myocardial Fibrosis	Cases With Record or Evidence of Hypertension		Others	
No. of cases	759		3,086	
With large fibrous patch	18		74	
Rate %		*2·4%*		*2·4%*
With smaller multiple scars	122		172	
Rate %		*16·1%*		*5·6%*

TABLE IV.—*Proportions with Ischaemic Myocardial Fibrosis by Physical Activity of Occupation. Factor of Hypertension. 3,800 Non-coronary Deaths. Males Aged 45–70*

Age	Ischaemic Myocardial Fibrosis	Cases with Record or Evidence of Hypertension			Others		
		Occupation			Occupation		
		Light	Active	Heavy	Light	Active	Heavy
45<60	No. of cases	135	130	41	567	575	365
	With large fibrous patch	2	2	0	14	7	2
	Rate %	*(1·5%)*	*(1·5%)*	*(0%)**	*2·5%*	*1·2%*	*(0·5%)*
	With smaller multiple scars	29	12	2	25	18	12
	Rate %	*21·5%*	*9·2%*	*(4·9%)*	*4·4%*	*3·1%*	*3·3%*
	Total with ischaemic myocardial fibrosis	31	14	2	39	25	14
	Rate %	*23·0%*	*10·8%*	*(4·9%)*	*6·9%*	*4·3%*	*3·8%*
60–70	No. of cases	194	160	78	544	564	378
	With large fibrous patch	10	3	1	25	16	7
	Rate %	*5·2%*	*(1·9%)*	*(1·3%)*	*4·6%*	*2·8%*	*1·9%*
	With smaller multiple scars	42	23	11	46	43	24
	Rate %	*21·6%*	*14·4%*	*14·1%*	*8·5%*	*7·6%*	*6·3%*
	Total with ischaemic myocardial fibrosis	52	26	12	71	59	31
	Rate %	*26·8%*	*16·3%*	*15·4%*	*13·1%*	*10·5%*	*8·2%*

Tests of Significance

	Hypertensives	Others
Line 1	—*	0·02>p>0·01
,, 2	0·01>p>0·001	—*
,, 3	0·01>p>0·001	0·02>p>0·01
,, 4	—*	0·02>p>0·01
,, 5	0·05>p>0·02	—*
,, 6	0·01>p>0·001	0·02>p>0·01

This table amalgamates the "basal" and "high" coronary artery disease Groups C and B, and corresponds with Table I. 0 and 0%=No cases with ischaemic myocardial fibrosis.

Tests were for trends in percentages from "light" through "active" to "heavy" occupations (cf. footnote to Table I). * Trend not significant—i.e., $p>0.05$.

TABLE V.—*Coronary Artery Disease by Physical Activity of Occupation. 3,800 Non-coronary Deaths. Males Aged 45–70*

Coronary Artery Disease		"Basal" Group			"High" Coronary Artery Disease Group			All Non-Coronary Deaths		
		Occupation			Occupation			Occupation		
		Light	Active	Heavy	Light	Active	Heavy	Light	Active	Heavy
	No. of cases:	995	1,034	668	445	395	194	1,440	1,429	862
(1) Coronary atherosclerosis present	Rate %	85	82	82	91	90	86	87	84	83
(2) Much coronary atherosclerosis with focal obstruction ("severe disease")	Rate %	10	9	10	24	17	22	14	11	13
(3) Much coronary atherosclerosis without focal obstruction	Rate %	5·7	6·0	4·6	9·0	8·4	9·3	6·7	6·6	5·7
(4) Calcification present	Rate %	19	18	18	32	26	31	23	20	21
(5) Focal obstruction present including	Rate %	21	16	19	34	28	32	25	19	22
(6) Complete or near-complete occlusion of a main coronary artery	Rate %	3·7	3·0	2·5	10·3	7·3	5·7	5·8*	4·2	3·2

The figures in the last panel cannot be used directly as indicators, however crude, of the overall prevalence of coronary artery disease, and of its various manifestations, in the whole middle-aged male population of Britain. Even if the dead can be taken at all to represent the situation in the living, it must be remembered that deaths from clinical coronary heart disease (Group A) have not been considered so far. The great majority of these would of course show severe coronary artery disease, coronary occlusions, etc.; and, whatever proportion of such cases were added to set up a "model" of the total population, the totals of all 6 indicators, except (3), in the last panel would surely be raised. On the other hand, *deaths* from severe hypertension, as in Group B, are very likely *over*-represented. However that may be, it seems probable from what is known of the occurrence of clinical coronary heart disease in different occupations that the excess here reported of coronary occlusions among light occupations may be an underestimate. By the same token, there may well be some excess of severe coronary artery disease among light workers in the population as a whole.

* $0.02>p>0.01$.

trend. But the picture is quite different in the smaller/multiple scars. Among the hypertensives the prevalence of this focal myocardial fibrosis was very high in light workers —22% of these patients aged 45–70 (*21.5%* and *21.6%*) showed it. This rate is higher than that found in the active and heavy workers with hypertension, and much higher than in all with no record or evidence of hypertension (Others in Table). The effects are again clearer at 45<60 years; the light occupations showed these small scars almost *three* times more often at this age than the rest with hypertension, and *six* times more than the others without hypertension. At 60–70 years the figures are *one and a half* times, and *three* times, respectively. Indeed, this special excess of small, multiple scars *in light workers* with hypertension is largely responsible for the higher overall rate of such scars seen in hypertensives as a whole (Table III) when they are compared with the "others." (These "others" without record or evidence of hypertension, it is interesting, showed little variation of focal myocardial fibrosis with occupation among themselves, but what trend there was is also in the expected direction.) In brief, however,

The physical activity factor is clearly evident in the occurrence of smaller/multiple scars only in association with hypertension. At ages 45–70, light workers with hypertension showed these scars twice as often as active and heavy workers with hypertension, and five times more than all without record or evidence of hypertension. The excess in light occupations is, again, greater at 45<60 years than at 60–70.

Coronary Artery Disease

The next question, of course, is whether these various occupational differences in the prevalence of ischaemic heart disease are associated with corresponding differences in the prevalence of coronary artery disease and, in particular, of coronary narrowing. The pathogenesis of ischaemic myocardial fibrosis may be regarded for the present as coronary insufficiency, and the basic pathology is "atheroma" or "atherosclerosis" (the terms are interchangeable in Britain —and equally unsatisfactory) with focal coronary obstruction. Most ischaemic scars, it will be recalled, were associated with topical coronary narrowing, the large fibrous patches more commonly with complete or near-complete occlusions, the smaller/multiple scars with lesser degrees of coronary narrowing.

Statistical analysis of the condition of the coronary arteries in the 5,000 reports has only been started, and it will inevitably be on less sure ground than with myocardial fibrosis. Meanwhile, Table V presents some preliminary indices of macroscopic disease in the main arteries and large branches[6 12 16 17 18 23 26 27 28 39 42 47 67] firstly for the basal group C and then for the high coronary artery disease group B, the main classification of the inquiry as a whole. These are the indices:*

(1) The presence of any reported coronary atheroma. Macroscopic intimal disease was reported in 85% of the cases in the light occupations of the basal group, 82% in the active occupations, etc.

(2) The proportion with severe coronary atherosclerosis, using mainly a simple quantitative five-point scale of "none," "little," "moderate," "much," "indefinite" disease. The minimum to qualify as "severe" was (*a*) "much" atheroma throughout the coronary arteries with large or confluent plaque formation—superficial flecking or streaking alone did not count—showing also (*b*) some focal obstruction.

(3) The presence of much mural disease without encroachment upon the lumen. Cases with arterial dilatation were also included here.

(4) The presence of calcification.

(5) The proportion with coronary obstruction—that is, lumen stenosis or narrowing of any degree; and including

(6) Complete occlusion or near-complete (e.g., "admitting fine probe only") of a main coronary artery (left, left anterior descending, circumflex, right). This alone was called "coronary occlusion."

Diffuse intimal fibrous thickening, by itself, was ignored.

There is much in Table V, but attention is here paid only to the frequency of coronary artery disease by occupation. Both in the basal group and in the cases of the high coronary artery disease group—Table V corresponds to Table I but is set out horizontally—gross coronary artery disease (1), (2), (3), and (4) is exceedingly common: however, there is no occupational trend of any interest. Index (5) again reveals no material difference in the overall frequency of coronary obstruction among the occupation groups. In terms of one of the original hopes in the design of the inquiry the stability of these various indices of coronary artery disease is reassuring—if for other reasons disappointing! The first observation of note is in (6), the greater frequency of complete or near-complete occlusions in light occupations (5.8%) compared with heavy (3.2%). The rate of coronary occlusion, as defined, is about the same in light workers aged 45<60 as in heavy workers 10–15 years older (Table VI). Straightaway, however, it is obvious that the excess of occlusion in light workers is less than the excess of large healed infarcts already reported in Table II.

Comparison of the condition of the coronary arteries in cases with *hypertension* and in others showed much more atherosclerosis

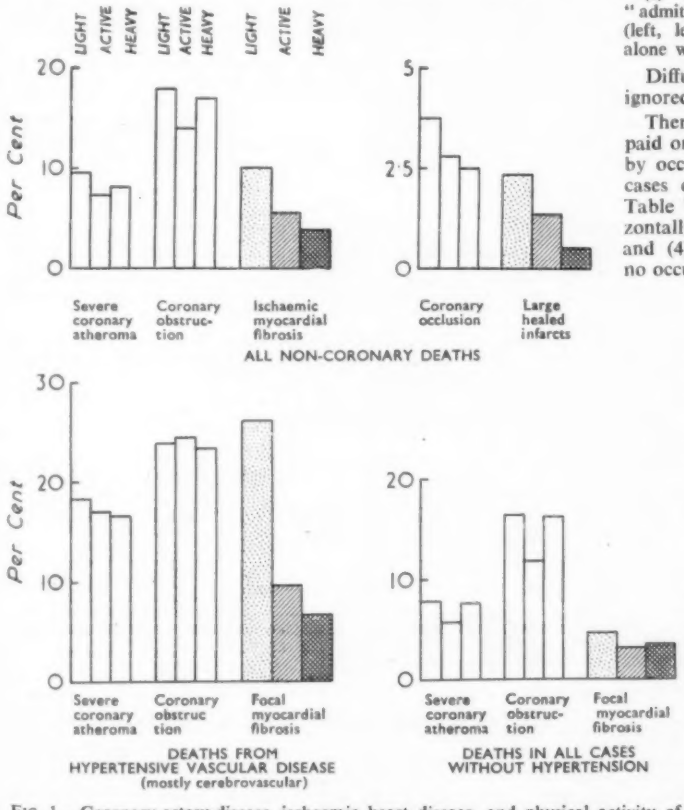

FIG. 1.—Coronary artery disease, ischaemic heart disease, and physical activity of occupation. 1,800 non-coronary deaths. Males aged 45<60 years.

*The Report of the World Health Organization's Study Group on the Classification of Atherosclerotic Lesions (*Wld Hlth Org. techn. Rep. Ser.*, 1958, 143) became available too late for use in this analysis.

TABLE VI.—*Coronary Occlusion. 3,800 Non-coronary Deaths. Men*

Ages	Occupation		
	Light	Active	Heavy
45<60	3·8%	2·8%	2·5%
60–70	7·6%	5·5%	3·9%

TABLE VII.—*Severe Coronary Atherosclerosis. 3,800 Non-coronary Deaths. Males Aged 45–70*

Cases	Occupation		
	Light	Active	Heavy
With hypertension	22%	19%	19%
No record or evidence of hypertension	12%	9%	12%

in the hypertensive throughout 45–70 years of age.[6 20 84] For example, the proportion with severe coronary atherosclerosis, as previously defined, was as shown in Table VII. The prevalence of coronary occlusions was higher in the hypertensive, and it was greatest again in the light occupations. There was no occupational trend, however, in the frequency of lesser degrees of coronary narrowing among the hypertensives; though, as stated above, these cases showed a strong light-heavy trend in the frequency of focal myocardial fibrosis, and the small/multiple scars are particularly associated with such lesser narrowing.

Fig. 1 illustrates these points in the most interesting cases, men under 60. If all such cases are taken together, there is no particular difference with occupation in the prevalence of severe coronary artery disease, or in the overall prevalence of coronary obstruction, but quite a clear trend in ischaemic scarring. There is a gradient with occupation in the frequency of complete or near-complete coronary occlusions—notice the change of scale—but a steeper one in the large healed infarcts. It is striking how, with similar occupational frequencies of coronary obstruction, the hypertensive cases (the most important cases in Group B have been used for this illustration—the deaths actually from hypertensive vascular disease, mostly cerebral) show a marked occupational difference in the frequency of focal myocardial fibrosis. On the other hand, in the cases without hypertension there are again similar prevalences of arterial obstruction in the occupation groups but, now, very little occupational trend in such scars. (The contrast with focal myocardial fibrosis is the same if the prevalence of lesser coronary narrowing alone is included.) It looks, then, as if much of the variation in ischaemic myocardial scarring with physical activity of work does not depend on occupational differences of, at any rate, *gross* coronary artery disease. Or, another way of looking at the data, there is no suggestion in the present material that habitual physical exertion materially affects coronary atheroma, but an indication that it is related to the frequency of coronary occlusion.*

**Hypertension.* We have shown that focal myocardial fibrosis was commoner in hypertensive cases than in those without record or evidence of hypertension and that, among the hypertensives, light workers showed substantially more of these small scars than did the active and heavy workers. There is another point of interest. In this material, the proportion of cases with hypertension among heavy workers, throughout 45–70 years of age but more so in the younger men, is smaller than among light workers. In Group C, at 45<60, 3% of the men in heavy occupations showed it, compared with 8% in light; in Group B, 39% compared with 50%.[69] "Following through" this observation from the Group C through Group B into Group A, it may be seen in Table XII (next footnote) that the proportion with hypertension in these deaths *from* coronary heart disease, etc., was lower in heavy occupations than the others. Broadly speaking, in the material as a whole the frequency of hypertension in heavy workers aged 60–70 was the same as in light workers of 45<60 years of age.

Two special factors, then, may be operating in relation to hypertension: heavy workers possibly have less of it; and light workers with hypertension may be specially liable to cardiac damage. The suggestion that the combination of high blood pressure and light occupation may be particularly important, may provide a "way in" for the study of the complicated relations of hypertension with coronary heart disease.

Occupation and "Social Class"

The distribution, in Britain, of mortality from coronary heart disease by social class is well known. First established in 1930–2,[86] the most recent figures (Table VIII) relate to 1949–53.

TABLE VIII

Social Class	Scotland[66 69] Males, Aged 15 and Over	England and Wales[23 57] Males, Aged 20–64
I	167	147
II	119	110
III	109	105
IV	85	79
V	79	89
All classes	100	100

The mortality in social class I (Osler's[52] "better classes") when adjusted for age, as in the above, is much higher than in the rest and about twice that in classes IV and V.

"Social class" is intended to reflect "general standing within the community," social class I including the leading professions and business, class III the craftsmen and skilled workers, and class V the unskilled. Classes II and IV are intermediate. It seems clear that, for men in the age range dealt with, "class" also provides an economic grading.

The 3,800 non-coronary deaths of the present inquiry were analysed by social class[59]: the present approach has the advantage that the "level" or "plane" of description and diagnosis is probably the same for all classes. The result in Table IX shows a steady fall in ischaemic myocardial fibrosis from 13.3% to 7.8%. This trend, however, disappears when the social classes are analysed in terms of the physical activity of the occupations in them. Table X(A), read *downwards*, shows that the frequency of the fibrosis in these light workers of similar ages is about the same in social classes I, II, III, and IV—that is, there is no

TABLE IX.—*Proportions With Ischaemic Myocardial Fibrosis by Social Class. 3,800 Non-coronary Deaths. Males Aged 45–70*

Social Class	No.	Proportion with Ischaemic Myocardial Fibrosis
I	98	13·3%
II	510	12·1%
III	1,847	10·5%
IV	605	9·2%
V	683	7·8%

The trend of the proportions with ischaemic myocardial fibrosis is statistically significant ($p < 0.01$).

Occupations were allocated to social class in accordance with the General Register Office *Classification of Occupations*, 1950.[58] 102 cases could not be so allocated because of insufficient information.

TABLE X.—*Proportions with Ischaemic Myocardial Fibrosis by Social Class and Physical Activity of Occupation. 3,800 Non-coronary Deaths. Males Aged 45–70.*

Social Class	Light Occupations %	Active Occupations %	Heavy Occupations %	All %
(A) Ischaemic Myocardial Fibrosis by Social Class and Physical Activity of Occupation:				
I	13·7	(0)	—*	13·3 } 12·3
II	13·4	9·2	(0)	12·1 }
III	13·8	8·0	8·2	10·5
IV	13·5	10·1	4·9	9·1
V	8·9	9·0	7·1	7·8
All	13·4	8·7	6·8	10·0
(B) Large Healed Infarcts by Social Class and Physical Activity of Occupation:				
I and II ..	4·3	(2·1)	(0)	3·8
III	3·2	1·8	(1·2)	2·3
IV	(3·6)	2·1	(1·5)	2·3
V	(2·2)	(2·2)	(1·0)	1·5
(C) Focal Myocardial Fibrosis by Social Class and Physical Activity of Occupation:				
I and II ..	9·1	6·9	(0)	8·6
III	10·6	6·2	6·9	8·2
IV	9·9	8·0	3·4	6·8
V	6·7	6·7	6·1	6·3

*No cases at all.

variation with social class and, incidentally, no indication of the particular excess seen in the national mortality data among social class I. There is again no class trend in the active occupations (middle column of Table X(A)) and less than none in the heavy. But reading Table X(A) *across*, the light-heavy trend previously reported is pretty clear *within* each social class, the light occupations showing more with scars than the active in class II, and the light in class III and class IV a higher prevalence than the active and heavy in these classes. That is to say, among men of comparable social-economic circumstances, those in light occupations showed a clear excess of ischaemic myocardial fibrosis.[9 43] As would be expected—Tables X(B) and (C)—the reduction in the frequency of fibrosis that occurs with physical activity of occupation *within* the social classes is more evident for the large healed infarcts; though the numbers in Table X(B) are impossibly small.

The irregularities in these tables are also interesting. Social class V stands out on its own, both in showing low rates among light workers and in showing little trend with occupation. It is just in these men that the classification of occupations by "activity" is at its weakest. On the one hand, the light occupations—for example, lift attendant, night watchman—are reserved mostly for disabled persons; therefore the last and "light" job, more than in other classes, is apt to be an inaccurate indicator of the main or usual job during working life. On the other hand, all "general labourers" were perforce graded as "heavy" workers, though, as is well known, many an elderly "labourer," officially or unofficially disabled, does little more than odd jobs on a building site and the like, and may have been so occupied for years before his death. There is an irregularity in social class III because some very heavy workers—for example, stonemasons and boilermakers—have a high prevalence of scars, high for heavy workers; a hint here, perhaps, of the dangers of *too much* physical activity.[44] The rate for heavy occupations in class IV is particularly low because agricultural workers show little ischaemic fibrosis—little even for heavy workers. These special features of classes III and IV persist when the prevalence of scarring in these particular occupations is compared also with that of other heavy workers in the same

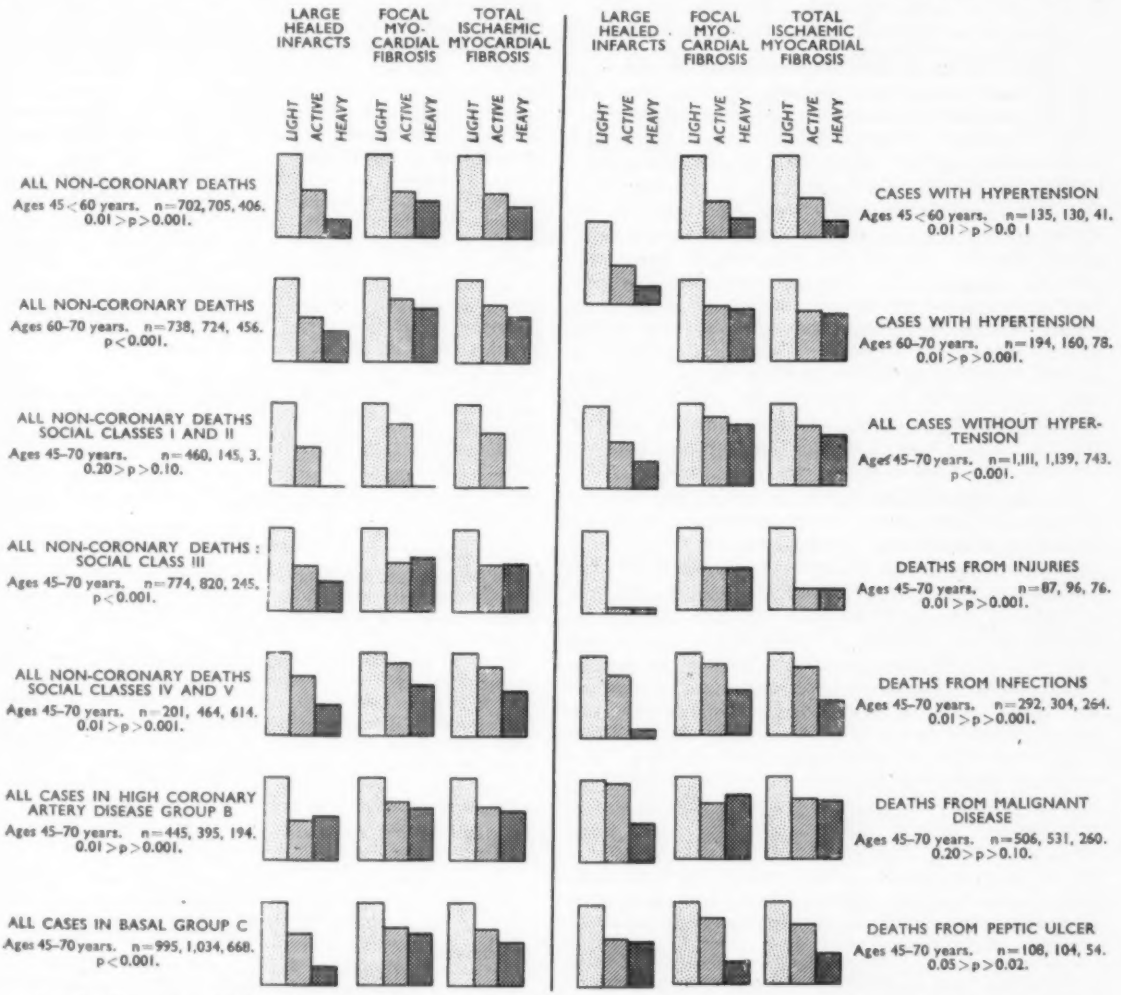

FIG. 2.—Frequency of ischaemic myocardial fibrosis, by physical activity of occupation. 3,800 non-coronary deaths. Males aged 45–70 years. In each block of three columns the first column is the rate among light occupations regarded as 100%. In the second column (active occupations) and the third column (heavy) the rates have been recalculated as proportions of the rate among light occupations.

In each line the first block represents the large fibrous patches; the second block represents the smaller/multiple scars; and the third is the total of ischaemic myocardial fibrosis.

n gives the numbers of cases in light, active, and heavy occupations in that order. The test of significance applies to the total of ischaemic myocardial fibrosis. In deaths from injuries active and heavy occupations have been amalgamated.

sets of necropsy reports, the kind of internal "control" that is so important in this type of study.[40]

In brief, *in this material* there is no evidence of any important "class" factor. Most of the social class trend in ischaemic myocardial fibrosis seems to arise from the distribution of "light" and "heavy" workers among the classes (Table XI), though there is evidence also of other and it may be more specific occupational factors affecting the class rates. The association of ischaemic myocardial fibrosis with physical activity of work in these data seems to be independent of standards of living, including obviously in the present instance levels of education and skill and possibly also of responsibility.

TABLE XI.—*Distribution of Occupations Within the Social Classes*

Social Class	Percentage of			Total
	Light Occupations	Active Occupations	Heavy Occupations	
I	97	3	—	98
II	72	28	1	510
III	42	44	13	1,847
IV	18	47	34	605
V	13	26	60	683

Summing up the 3,800 Non-coronary Deaths

Fig. 2 sums up the main findings. In each block the rate of ischaemic myocardial fibrosis in the light occupations is regarded as 100%, and the rates in active and heavy occupations are calculated as proportions of this. In each line the first block illustrates the prevalence of the large fibrous patch, the middle block that of the smaller scars, and the third is the total of ischaemic myocardial fibrosis. (In the first two lines of the second column dealing with hypertensive disease the data have been amalgamated for 45–70 years of age in the large healed infarcts, but distinguished by the two age groups in focal myocardial fibrosis.) There is, of course, considerable overlapping in these various extracts from the data, and some of the numbers—the total is given in each line for light, active, and heavy in that order—are small. The tests of statistical significance apply to the total with scars in each line.

The consistency of the pattern is striking and makes it unlikely that the association of ischaemic myocardial fibrosis, and particularly the large healed infarcts, with physical activity of occupation is the product of some gross bias in this necropsy material. There is quite conceivably an association between ischaemic myocardial fibrosis and the chances of dying and/or undergoing necropsy. But it is less conceivable that such an association could be systematically greater in light occupations than heavy, so that with equal real prevalence of fibrosis among occupations the rate would appear higher in the light. And it is difficult to conceive how such a bias could be effective in the wide variety of disease (and other categories) illustrated in Fig. 2. But, of course, bias can be "built-in" in goodness knows how many ways, and no individual study can deal with all of even the recognized sources. Other studies will need to be done, and also on large numbers, to repeat these observations and to permit still further and quite different subdivisions of the data.

Evidence from 1,200 Deaths from Coronary Heart Disease

As stated before, about 1,200 of the 5,000 reports in the inquiry were on deaths in which coronary heart disease was the main cause—coronary heart disease by itself, or coronary heart disease with hypertension or with other pathology (for example, the post-operative cases)—together with a small number of less-defined though related cardiac conditions. These 1,200 will be described elsewhere. Much less can be made of them because they raise acutely the intractable problem of selection of cases; problems that are of less moment, as just discussed, in conditions like ischaemic myocardial fibrosis which are not the main cause of death and are incidental and often chance findings at necropsy. Moreover, no base or denominator can be defined for the estimation of frequency *rates* of coronary heart disease—for example, by type of occupation. Less effort was therefore made to obtain a good national sample. Thus no request for co-operation was made to the coroners' pathologists in Greater London; though in the provinces many coroners' cases were included in the series of 25, and there were a fair number also, as a matter of fact, in the Metropolitan hospitals' series. However, the 1,200 deaths from coronary heart disease can be classified by occupation and ratios comparing the actual number of cases in each of the three occupation groups can be calculated. This was done.

There were 482 deaths from coronary heart disease and related conditions in light workers, 436 in active workers, and 230 in heavy workers, a ratio of 1.0:0.9:0.48; and there is little doubt, from previous inquiries by the unit,[39 43 42] that if the London area had been fully represented the excess of light occupations among deaths from coronary heart disease would have been greater still. Meanwhile it may be noted that the trend with occupation in deaths from coronary heart disease is greater in the cases with hypertension than in the others.

Fig. 3 sets out the occupational ratios of the coronary heart disease and related deaths (Group A), and for completeness the ratios of the cases with ischaemic myocardial fibrosis in the high coronary artery disease group B, then of the cases with such fibrosis in the basal group C. Fig. d gives the ratio (using again the numbers in light, active, and heavy occupations) of all these cases with evidence of ischaemic heart disease in Groups A, B, and C added together—that is, in the whole series of 5,000. This is 1.0:0.84:0.43. Fig. 3e is for the rest of the 5,000 reports, those showing no evidence of ischaemic heart disease—1.0:1.05:0.64; and this ratio is plainly not of a kind with the previous ($p<0.001$). For what such evidence is worth, then—and this is by no means the right way of asking this particular question—there is indication of higher mortality from clinical coronary heart disease among light workers.*

Discussion

An association has been demonstrated between physical activity/inactivity of work and one form of coronary heart disease, ischaemic myocardial fibrosis. Explanation of this may be attempted along several lines. First, that light occupation increases the incidence of ischaemic myocardial fibrosis, heavy jobs are protective. Second, that the association is effect rather than cause; on account of disability from myocardial ischaemia men give up heavy jobs for light ones and a higher prevalence of scarring is thereby created among light workers. Third, that the association is indirect:

*Other sums can be done with the data if required:

TABLE XII.—*Number of Cases of Ischaemic Heart Disease in a National Sample of 5,000 Necropsies. Males Aged 45–70*

Occupation	"Coronary" Deaths, Etc.		Non-Coronary Deaths, with Ischaemic Myocardial Fibrosis		Non-Coronary Deaths, With *No* Ischaemic Myocardial Fibrosis	Total
	Hypertension Present	Others	Large Healed Infarcts	Focal Myocardial Fibrosis		
Light (No.) ..	145	337	51	142	1,247	1,922
Active (No.) ..	127	309	28	96	1,305	1,865
Heavy (No.) ..	51	179	10	49	803	1,092
Total ..	1,148		376		3,355	4,879

160 cases were excluded for one reason or another, cf., Table I.

for example, susceptibility to coronary heart disease and individual choice of job may both be the product of host factors in constitution (and previous experience); or physical activity/inactivity may be reflections merely of the nervous strain of jobs, and it is this that really matters in coronary heart disease. All these processes, it could reasonably be proposed in the present state of knowledge, contribute to the community picture of coronary heart disease; but, of course, the first is the most interesting.

The present study sheds no light on personality factors, though we hope other inquiries in which we are engaged—on somatotype and occupation, for example—will do so.[44] No attempt has yet been made to classify the 1,700 different job descriptions in terms, say, of responsibility, of nervous strain—and emotional support. This might be done; but it is an appalling prospect, and the similarity of the rate of fibrosis among the professional and business men of class I to that found in the semi-skilled light workers of class IV does not encourage us to try. The study of psychological stress in relation to coronary heart disease still lacks an appropriate method (we have long thought that a forward-looking study among doctors from their late thirties or early forties is the most hopeful). The possibility that the high prevalence of fibrosis in light jobs is the result of transfer by men into these *because* of coronary insufficiency has not been directly considered. It can only be said that the evidence available gives no hint that such transfer, which must surely be common, explains all or even much of the occupational distribution found. Thus the excess of scarring among light workers is no greater at 60–70 years of age than at 45<60, and, indeed, for the large patches it is more evident in the younger men. Moreover, it may again be pertinent that the rate among the light occupations of social classes I and II, drift into which from heavy jobs in unlikely, is just as high as that in class III, where such drift is more likely, and class IV, where it is very likely. In social class V itself there was little if any excess among the light occupations, which is as reassuring as it was unexpected; because, as already said, it is just these jobs—messenger, lift attendant, night watchman, and the like—that "disabled" manual workers so often select, and drift into, which for lesser impairment is also very likely. But this difficult and important problem needs to be tackled in other ways: an attempt is now being made in this unit, for example, to determine the prevalence of quite silent coronary heart disease by electrocardiographic study of workers with contrasting physical activity of jobs.

FIG. 3.—Ratios of the number of cases of ischaemic heart disease in the three occupational groups, the number in light occupations being regarded as 1. National sample of 5,000 necropsies. Males aged 45–70. Scotland, England and Wales, 1954–6. (*a*) Group A: Deaths from ischaemic heart disease, etc. (*b*) Ischaemic myocardial scars in cases of Group B. (*c*) Ischaemic myocardial scars in cases of Group C. (*d*) Showing *a*, *b*, and *c* added together. (*e*) All the cases without ischaemic heart disease.

Restatement of Hypothesis

Another piece of evidence has thus been provided in this report that confirms the general hypothesis, and using on this occasion quite different material from before. In the present data as a whole, and in every sizable category of it, *there was a lower prevalence of ischaemic myocardial fibrosis among men who had been in physically active and heavy jobs than among those in sedentary and light jobs.* Study of the detailed morbid anatomy of this social difference supports the second part of the original hypothesis. It is particularly in the prevalence of the large, often and for obvious reasons solitary, patch of fibrosis, the probable result it may be said of major and acute infarction (and homologue of sudden death in the bus driver?) that light workers shows an excess. The heavy workers had less ischaemic fibrosis altogether, and relatively more of it took the form of smaller patches and small, often very small, scars. That is to say, in this material *ischaemic myocardial fibrosis is not so severe in physically active and heavy* workers. But the prevalence of these minor forms of myocardial fibrosis also was lower in active and heavy than in light occupations; which rather suggests that the excess of angina previously noted in physically active men (bus conductors and postmen) is more likely to be a matter of symptom formation, of the disease being elicited and made manifest in them by their physical effort, rather than of an absolute excess of any particular pathology in active workers.[43]

Evidence can now be advanced relating physical activity of occupation to the incidence of coronary heart disease, to sudden death and other rapidly fatal cardiac infarction, to the prognosis in the survivors of the first clinical episode, to the prevalence of the disease, to total coronary mortality in middle-age, and to several forms of ischaemic myocardial fibrosis. The time seems to have come, in view of the convergence of such varied and independent evidence, for a restatement of the general hypothesis in causal terms: *Physical activity of work is a protection against coronary (ischaemic) heart disease. Men in physically active jobs have less coronary heart disease during middle-age, what disease they have is less severe, and they develop it later than men in physically inactive jobs.*

It must be emphasized, however, that, overall, the evidence on this problem is quite conflicting.[2 5 7 9 11 12 23 24 27 34 45 58 63 64 66 69] In several studies coronary heart disease has been found to be associated with physical activity/inactivity of occupation in the expected way. In as many, no relationship was demonstrated, or an equivocal or opposite one; and why this is so is still quite unclear. Different methods are being used by different investigators and different aspects of the disease are being studied. Moreover, the "epidemic constitution" may be different in the U.S.A. from the U.K.—the important causes may be present in different degrees and in different combinations.[22]

Some *speculations* may be worth airing here. The diminishing physical activity of work during the present century may be one of the causes of the increasing incidence of coronary heart disease that seems to be occurring, and, if the increase is as modest as is now often suggested, a principal cause. This question might be studied through the historical experiences of "underdeveloped" populations becoming "westernized." If it is argued that constitution and mesomorphy is the crucial variable, unexpressed mesomorphy, the disuse of large-muscle masses, may be said to be one of the characteristic biological consequences of industrialization. Then, it may be asked whether regular physical activity *outside* work protects against coronary heart disease in middle-age. There is no information, meanwhile, on the relations, if any, between physical exertion in leisure, for example, and the incidence or prevalence of coronary heart disease; but plainly this is the main implication of observations such as the present for preventive medicine, and means of testing such a hypothesis must be found. Typical of to-day's problems in epidemiology, this will involve *ad hoc* studies of large numbers of individuals; and even preliminary indirect studies of coronary heart disease and leisure activities in ready-made social groups such as the social "classes" cannot be made.

A final speculation may be advanced that *habitual physical activity is a general factor of cardiovascular health in middle-aged men* since it may be related to blood lipid levels, to clotting and to fibrinolysis, to diabetes, to hypertension and its complications, to coronary occlusion, and to ischaemic heart disease.[3 10 20 25 28 29 30 31 35 40 59 62 66] Regular physical exercise could be one of the "ways of life"

that promote health in middle-age, and ischaemic heart disease may be in some degree a deprivation syndrome, a deficiency disease.

Mechanisms of the Occupational Difference

Nothing corresponding to the differences with physical activity which have been found in experimental atherogenesis[31 80] were observed in the present material. Clearly the main causes of coronary atherosclerosis in man have to be sought elsewhere—for example, in hypertension and, the principal field of interest at present, in diet and lipid metabolism. There is more coronary occlusion among the light occupations, which is particularly interesting because the factor of intracoronary thrombosis may be particularly associated with these complications of atheroma[16 17 18 21] and the present findings may be another indication of the relationship between physical activity and intravascular clotting.[2 33 39 86] If, as many would argue, the pathogenesis of all degrees of coronary obstruction is the same, then, it would appear, the capacity to cope and to resolve such obstructions must vary with occcupation so that actual occlusion of large coronary vessels is less common in active and heavy workers than in sedentary and light workers. However that may be, the excess of coronary occlusion is inadequate to explain the excess of large healed infarcts in light occupations; and the other indicators of coronary artery disease so far studied do not help at all to account for the occupational distribution of the scarring. Mechanisms of the occupational differences in ischaemic myocardial fibrosis need therefore to be postulated that operate additionally to those of gross coronary artery disease,[10 32 33 58 63] in general and local haemodynamics, it may be, in neuro-hormonal mechanisms, in special relationships with hypertension, in the physiological capacity of the main arteries and branches, in intercoronary collateral circulation.[4 19 30 61 70] Recently it has been observed that effective collateral vessels in dogs with coronary obstruction develop more profusely if the dogs are exercised; functional myocardial hypoxia might be the mechanism relating physical activity to collateral formation.[19 20]

Distinction of Ischaemic Heart Disease from Coronary Artery Disease

In the first report of the present series[39] it was suggested that the recent history of coronary thrombosis/myocardial infarction on the one hand, and that of coronary atheroma on the other, are different. The former, there is good reason to believe, have increased during this century; there is no evidence whatever in Britain that the latter has, and, indeed, coronary atheroma may have declined here during the past 40 years.[59 66] The historical material, that is to say, suggests that ischaemic heart disease is not a simple, proportional function of coronary atherosclerosis. The evidence now presented goes further in dissociating the heart disease from the arterial disease, because it suggests that even when the latter is analysed into obstructive and non-obstructive processes nothing like a 1:1 relationship emerges between myocardial damage and the *obstructive* arterial disease. Social grouping of the pathological data (by occupation) shows substantial differences in the frequency of myocardial fibrosis which correspond only moderately to the frequency of coronary occlusions and correspond not at all to the frequency of lesser narrowing of the coronary lumen. Such identification of syndromes from undifferentiated clinical material—in this instance of ischaemic heart disease from coronary artery disease—is one of the uses of epidemiology, and theoretically is of much interest.[46]

A Word on the Method

Finally, it may be remarked that post-mortem reports are just about the most difficult medium for epidemiological analysis: many sources of bias in the material are known; as many, it must be assumed, are quite unknown. The use of necropsy data finds its main warrant in asking questions, such as the present report illustrates, that cannot be asked by any other method. But the limitations of any one set of data, with its inevitably imperfect "population" samples and incomplete ascertainment of disease, make it very necessary that studies are repeated in quite different situations.

Summary and Conclusions

This report is one of a series on the epidemiology of coronary disease, and it continues the study of coronary (ischaemic) heart disease in relation to physical activity of work.

The hypothesis was previously stated that *men in physically active jobs have a lower incidence of coronary heart disease in middle-age than men in physically inactive jobs. More important, the disease is not so severe in physically active workers, tending to present in them in relatively benign forms.* The investigation now reported deals with the relations between physical activity of work and the frequency of ischaemic myocardial fibrosis in a sample of 3,800 middle-aged men dying from causes other than coronary heart disease.

All departments of morbid anatomy in the hospitals of the National Health Service of Scotland, England, and Wales were invited to take part in a national necropsy survey during 1954–6 by sending particulars in standard form of the naked-eye findings on the coronary arteries, the myocardium, and other specified items for a consecutive series of 25 males aged 45–70 years coming to necropsy. 206 departments co-operated, more than 85% of those eligible. About 5,000 reports were received, made up in round numbers thus: 1,200 deaths from coronary heart disease, etc. (Group A); 1,000 deaths from conditions with a specially high prevalence of coronary artery disease—for example, deaths caused by hypertension and its complications, deaths in diabetics, deaths from arterial disease in other sites (Group B); and, the remainder, 2,800 deaths from miscellaneous conditions, their main causes having no particular association with coronary artery disease—for example, injuries, infections, cancer (Group C). Groups B and C comprise 3,800 non-coronary deaths.

Two broad types of *ischaemic myocardial fibrosis* in the left ventricle and interventricular septum are described: (1) the large, discrete, often solitary patch which is probably the end-result of major and acute infarction and is associated particularly with complete or near-complete occlusion in a main coronary artery (90 cases among the 3,800 non-coronary deaths); and (2) smaller, commonly multiple scars, the result, it may be, of more chronic and less severe ischaemia, and occurring in hearts showing usually lesser focal narrowings of coronary arteries or branches (290 cases).

Cases were classified as "*hypertensive*" or "*other*" on the basis of the clinical and pathological information provided. About half the cases in Group B and 10% of those in Group C were thus regarded as hypertensive. The large healed infarcts—type 1 fibrosis above—were found equally in hypertensive and other cases; focal myocardial fibrosis of type 2 was commoner in hypertensive cases than in those without record or evidence of hypertension.

The last *occupation* of each man was graded on a three-point scale in terms of the physical activity the job typically involved as "light," "active," or "heavy."

Relation of Fibrosis to Occupation.—Ischaemic myocardial fibrosis in these 3,800 necropsies was commoner in the light occupations than in the active and heavy. Scarring among light workers aged 45<60 was as common as in heavy workers 10 to 15 years older.

The two main types of ischaemic fibrosis were differently related to physical activity of occupation:

The *large healed infarcts*, type 1 above, showed a strong gradient with occupation, being *three* times commoner in light workers than in heavy workers overall; *four to five* times commoner at 45<60 years of age, and *two to three* times commoner at 60–70 years. The excess of these severe ischaemic lesions in light workers was evident in Group B and in Group C, in hypertensive cases as in others, in every sizable medical and social category that was identified.

Focal myocardial fibrosis, type 2, was strongly associated with occupation only in hypertensive cases. Under 60 years of age, the light occupations among the hypertensives showed these small, multiple scars almost *three* times more often than active and heavy workers with hypertension, and about *six* times oftener than all without record or evidence of hypertension. The corresponding figures at 60–70 years of age were *one and a half* and *three* times.

In brief, ischaemic myocardial fibrosis was commoner in light occupations and it appeared earlier in them. It was also more severe among light workers, particularly at younger ages.

Coronary Artery Disease.—The pathological basis of ischaemic myocardial fibrosis is coronary "atheroma" or "atherosclerosis" with impairment of the coronary circulation. In the present data the overall prevalence of coronary atheroma was exceedingly high, and, little, moderate, or much, it did not vary with physical activity of occupation. Coronary narrowing was similarly common in all occupation groups. But actual occlusion of a main coronary artery, complete or near-complete, was commoner in sedentary and light workers than in the active and heavy. This excess of coronary occlusion was seen in the younger men and older, in hypertensive cases as in those without record or evidence of hypertension. In general, the frequency of coronary occlusion in light workers aged 45<60 was the same as that in heavy workers aged 60–70.

The main results of the inquiry may therefore be stated as follows: atheroma of coronary walls, no relationship with physical activity of occupation; occlusion of coronary lumen, some relationship; ischaemic myocardial fibrosis, much relationship.

Ischaemic Heart Disease and Coronary Artery Disease. — The excess of coronary occlusion among the light occupations was smaller than the excess of large healed infarcts found in them. Among hypertensive cases there was no trend with occupation in the frequency of lesser degrees of coronary narrowing, although, as stated, the frequency of focal myocardial fibrosis was greater in light workers with hypertension than in active and heavy workers with hypertension. That is to say, in the presence of coronary narrowing and occlusion light occupations showed more ischaemic lesions of the myocardium than did active and heavy workers. Analysis of this sample of pathological data by social (occupation) categories thus discloses only very limited correlation between the frequency of myocardial scarring and the condition of the coronary arteries. This is a further suggestion that ischaemic heart disease is not a simple function of coronary artery disease.

Hypertension was less common and occurred at later ages (10–15 years later) in the heavy occupations than in the rest; the excess of coronary occlusions in light workers was seen in hypertensive cases as in the others; a specially high prevalence of small ischaemic myocardial scars in light workers with hypertension has been described. There are suggestions thus of multiple connexions between physical activity of occupation and the blood pressure which need to be followed up.

The expected trend of ischaemic myocardial fibrosis with *social class* was found, the rate falling from 13.3% in class I through 10.5% in class III to 7.8% in class V. This trend, however, disappeared when the social classes were broken down into categories of physical activity, and the occupations of which each class is composed were graded as "light," "active," or "heavy." Light workers in classes I, II, III, and IV all had similar prevalence of ischaemic scarring, and there was no class trend in the fibrosis among active workers or in heavy workers. On the other hand, the relationship of fibrosis to physical activity of occupation was independent of social-economic circumstances, being evident within single social classes: light occupations in class II showed more ischaemic fibrosis than the active in that class, light skilled workers a higher rate than the active and heavy occupations in class III, the light occupations of class IV more scarring than the active and heavy in that class. The overall trend with social class in this material is largely a function of the different proportions of light and heavy workers in the different classes.

Evidence has now been produced relating several aspects of clinical and subclinical coronary heart disease to physical activity of work. The general *hypothesis* may therefore be restated in *causal* terms that *physical activity of work is a protection against coronary (ischaemic) heart disease. Men in physically active jobs have less coronary heart disease during middle-age, what disease they have is less severe, and they develop it later than men in physically inactive jobs.* Since there are suggestions of other connexions between physical activity of work and cardiovascular disease of middle-age, and multiplying evidence from laboratory experiment of the beneficial effects of exercise on relevant cardiovascular physiology and pathology, the *speculation* may be advanced that habitual physical activity is a general factor of cardiovascular health in middle-age, and that coronary heart disease is in some respects a deprivation syndrome, a deficiency disease. In the present material the hearts of sedentary and light workers showed the pathology of the hearts of heavy workers 10–15 years older.

Perspective.—Coronary heart disease among heavy workers, though less common, less severe, and occurring later than among light workers, is nevertheless common enough to constitute a major health problem in them: absolutely; and in comparison with the greater freedom from the disease heavy workers, like the rest of the population, seem to have enjoyed earlier this century and in many countries apparently still enjoy.

We are greatly obliged to many for their participation and help in this inquiry: to the pathologists, and their medical and lay colleagues, of the hospitals listed in the Appendix, with associated hospitals, for a prodigious amount of painstaking work, carried out often, we know, in circumstances of considerable difficulty; to Dr. K. Ball, Professor T. Crawford, Dr. I. Doniach, Professor J. Duguid, Professor G. L. Montgomery, Dr. M. F. Oliver, Professor D. S. Russell, and Dr. C. S. Treip for advice on the design of the Report Form and/or pilot work; Dr. R. Murray, formerly H.M. Medical Inspector of Factories and now of the I.L.O., and Dr. D. Turner, of the Medical Research Council's Environmental Hygiene Research Unit, for the classification of occupations; the Factory Department of the Ministry of Labour and Dr. E. R. Bransby, of the Ministry of Health, for advice on this problem; Dr. Richard Doll and Professor A. Bradford Hill for access to

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APPENDIX: PRINCIPAL PARTICIPATING HOSPITALS

SCOTLAND

NORTHERN REGION:
Royal Northern Infirmary, Inverness.

NORTH-EASTERN REGION:
Teaching Hospitals: Aberdeen Royal Infirmary; Woodend General Hospital, Aberdeen.

EASTERN REGION:
Teaching Hospitals: Dundee Royal Infirmary; Maryfield Hospital, Dundee; Perth Royal Infirmary.

SOUTH-EASTERN REGION:
Teaching Hospitals: Royal Infirmary, Edinburgh; Western, Northern, and Eastern General Hospitals; Leith Hospital.
Cameron Hospital, Windygates, Fife.

WESTERN REGION:
Teaching Hospitals: Western Infirmary, Glasgow; Royal Infirmary, Glasgow; Victoria Infirmary, Glasgow; Southern General Infirmary, Glasgow; Stobhill Hospital, Glasgow.
Kilmarnock Infirmary; Royal Infirmary, Dumfries; Stirling Royal Infirmary.

ENGLAND

Teaching Hospitals.—Manchester Royal Infirmary; Liverpool Royal Infirmary; Royal Victoria Infirmary, Newcastle upon Tyne; Queen Elizabeth Hospital, Birmingham; Accident Hospital, Birmingham; the General Hospital, Birmingham; Bristol Royal Infirmary; Addenbrooke's Hospital, Cambridge; Radcliffe Infirmary, Oxford.

Manchester Region.—Royal Lancaster Infirmary; Westmorland County Hospital, Kendal; Royal Infirmary, Blackburn; General Hospital, Burnley; Bolton Royal Infirmary; Hope Hospital, Salford; Salford Royal Hospital; Crumpsall Hospital, Manchester; Park Hospital, Davyhulme; Withington Hospital, Manchester; Stockport Infirmary; Macclesfield Hospital.

Liverpool Region.—County Hospital, Whiston; Walton Hospital, Liverpool; Sefton General Hospital, Liverpool; General Hospital, Birkenhead; Chester Royal Infirmary.

Newcastle Region.—Newcastle General Hospital; General Hospital, South Shields; Preston Hospital; Hexham General Hospital; Royal Infirmary, Sunderland; Shotley Bridge General Hospital; Dryburn Hospital, Durham; Bishop Auckland General Hospital; Sedgefield General Hospital; Darlington Memorial Hospital; West Hartlepool General Hospital; Cumberland Infirmary, Carlisle.

Birmingham Region.—Selly Oak Hospital, Birmingham; Dudley Road Hospital, Birmingham; Staffordshire General Infirmary; City General Hospital, Stoke-on-Trent; North Staffordshire Royal Infirmary; Walsall General Hospital; West Bromwich and District General Hospital; the Royal Hospital, Wolverhampton; Royal Salop Infirmary, Shrewsbury; Warwick General Hospital; General Hospital, Burton-on-Trent; Worcester Royal Infirmary; County Hospital, Hereford.

Leeds Region.—Scarborough Hospital; County Hospital, York; Hull Royal Infirmary; Clayton Hospital, Wakefield; Huddersfield Royal Infirmary; Royal Halifax Infirmary; St. James Hospital, Leeds; Victoria Hospital, Keighley; Otley General Hospital; Harrogate General Hospital.

Bristol Region.—Southmead General Hospital, Bristol; Frenchay Hospital, Bristol; Cheltenham General Hospital; Manor Hospital, Bath; Musgrove Park Hospital, Taunton; Royal Devon and Exeter Hospital; North Devon Infirmary; Torbay Hospital, Torquay; Royal Cornwall Infirmary, Truro; St. Martin's, Bath; Redruth Miners' and General Hospital, Camborne; West Cornwall Hospital, Penzance.

Sheffield Region.—City General Hospital, Sheffield; St. Helen Hospital, Barnsley; Doncaster Royal Infirmary; Chesterfield Royal Hospital; Derbyshire Royal Infirmary; Nottingham General Hospital; Leicester Royal Infirmary; Lincoln County Hospital; Grimsby General Hospital; Leicester General Hospital; Victoria Hospital, Worksop.

Oxford Region.—Royal Berkshire Hospital, Reading; Kettering General Hospital; Victoria Hospital, Swindon.

East Anglia Region.—Newmarket General Hospital; West Suffolk General Hospital; Ipswich and East Suffolk Hospital; Borough General Hospital, Ipswich; Norfolk and Norwich Hospital.

London Teaching Hospitals.—Charing Cross Hospital; Guy's Hospital; London Hospital; King's College Hospital; Royal Free Hospital; St. Bartholomew's Hospital; St. George's Hospital; St. Mary's Hospital, Paddington; St. Thomas's Hospital; University College Hospital; West London Hospital; Royal Marsden Hospital; Hammersmith Hospital.

North-west Metropolitan Region.—Bedford General Hospital; Luton and Dunstable Hospital, Luton; Lister Hospital, Hitchin; Canadian Red Cross Memorial Hospital, Taplow, Bucks; King Edward VII Hospital, Windsor; Barnet General Hospital; St. Albans City Hospital; Peace Memorial Hospital, Watford; Hillingdon Hospital, Uxbridge; West Middlesex Hospital, Isleworth; King Edward Memorial Hospital, Ealing; Central Middlesex Hospital; Willesden General Hospital; Royal Northern Hospital; the Royal London Homoeopathic Hospital; Whittington Hospital.

North-east Metropolitan Region.—Chase Farm Hospital; Prince of Wales Hospital; Bethnal Green Hospital; Hackney Hospital; Mile End Hospital; St. Andrew's Hospital, Bow; Queen Mary's Hospital, Stratford; Whipps Cross Hospital; Oldchurch Hospital; Southend General Hospital; Rochford General Hospital; St. Margaret's Hospital, Epping; St. John's Hospital, Essex; Essex County Hospital, Colchester; Black Notley Hospital, Braintree.

South-east Metropolitan Region.—St. Olave's Hospital; Miller General Hospital; St. Alfege's Hospital, Greenwich; Lewisham Hospital; Brook General Hospital; Dreadnought Seamen's Hospital; Queen Mary's Hospital, Sidcup; West Hill Hospital, Dartford; St. Bartholomew's Hospital, Rochester; Kent and Canterbury Hospital; Ramsgate and Margate General Hospital; Buckland Hospital, Dover; Pembury Hospital, Kent; Queen Victoria Hospital, East Grinstead; Orpington Hospital; Farnborough Hospital; Bromley Hospital; Princess Alice Memorial Hospital, Eastbourne; St. Mary's Hospital, Eastbourne; Cuckfield Hospital, Haywards Heath.

South-west Metropolitan Region.—Lambeth Hospital; St. Mary Abbots Hospital; Kingston Hospital; St. Helier Hospital, Carshalton; St. Peter's Hospital, Chertsey; St. Thomas's Hospital, Godalming; Royal West Sussex Hospital; Worthing Hospital; Portsmouth and Isle of Wight Area Pathological Service, Central Laboratory, Portsmouth; Royal South Hants Hospital, Southampton; Poole General Hospital; Royal Hants County Hospital; Salisbury General Infirmary; County Laboratory, Dorchester; Royal Portsmouth Hospital; Royal Isle of Wight County Hospital; Southampton General Hospital.

WALES

Teaching Hospital.—Royal Infirmary, Cardiff.

Welsh Region.—Royal Gwent Hospital, Newport, Mon.; St. Woolos Hospital, Newport, Mon.; St. James Hospital, Tredegar; Caerphilly District Miners' Hospital; St. David's Hospital, Cardiff; St. Tydfil's Hospital, Merthyr Tydfil; East Glamorgan Hospital; Neath General Hospital; Morriston Hospital, Swansea; General Hospital, Swansea; West Wales General Hospital, Carmarthen; Pembroke County War Memorial Hospital, Haverfordwest; the Llandudno General Hospital; Royal Alexandra Hospital, Rhyl; Denbigh Infirmary; War Memorial Hospital, Wrexham; North Wales Mental Hospital, Denbigh.

REFERENCES

1 Achor, R. W. P., Futch, W. D., Burchell, H. B., and Edwards, J. E., *A.M.A. Arch. intern. Med.*, 1956, **98**, 162.
2 *Acta med. scand.*, 1956, Suppl. 315.
3 Astrup, T., *Lancet*, 1956, **2**, 565.
4 Baroldi, G., Mantero, O., and Scomazzoni, G., *Circulat. Res.*, 1956, **4**, 223.
5 Becker, B. J. P., *Lancet*, 1958, **1**, 1019.
6 Bell, E. T., and Hartzell, T. B., *J. med. Res.*, 1924, **44**, 473.
7 Björck, G., Overbeck, W., and Grönvall, C., *Cardiologia (Basel)*, 1954, **25**, 232.
8 Blumgart, H. L., Schlesinger, M. J., and Davis, D., *Amer. Heart J.*, 1940, **19**, 1.
9 Brown, R. G., Davidson, L. A. G., McKeown, T., and Whitfield, A. G. W., *Lancet*, 1957, **2**, 1073.
10 Brozek, J., *Geriatrics*, 1955, **10**, 469.
11 Chapman, J. N., Goerke, L. S., and Loveland, D. B., *Amer. J. publ. Hlth*, 1957, **47**, Special Suppl., p. 33.
12 Crawford, T., and Levene, C. I., *J. Path. Bact.*, 1953, **66**, 19.
13 Crawford, W., and Broadley, H., *The People's Food*. Heinemann, London, 1938.
14 Doll, R., and Hill, A. B., *Brit. med. J.*, 1950, **2**, 739.
15 —— —— ibid., 1952, **2**, 1271.
16 Duguid, J. B., *Lancet*, 1949, **2**, 925.
17 —— ibid., 1954, **1**, 891.
18 —— and Robertson, W. B., ibid., 1955, **1**, 525.
19 Eckstein, R. W., *Fed. Proc.*, 1956, **15**, 54.
20 —— *Circulat. Res.*, 1957, **5**, 230.
21 Edwards, J. E., *Bull. N.Y. Acad. Med.*, 1957, **33**, 199.
21a Enos, W. F., Beyer, J. C., and Holmes, R. H., *J. Amer. med. Ass.*, 1955, **158**, 912.
22 —— Holmes, R. H., and Beyer, J., ibid., 1953, **152**, 1090.
23 Epstein, F. H., Boas, E. P., and Simpson, R., *J. chron. Dis.*, 1957, **5**, 300.
24 Gopalan, C., and Ramanathan, K. S., *Lancet*, 1956, **2**, 1212.
25 Greig, H. B. W., ibid., 1956, **2**, 16.
26 Harrison, C. V., and Wood, P., *Brit. Heart J.*, 1949, **11**, 205.
27 Kennedy, A. C., *Scot. med. J.*, 1957, **2**, 420.
28 Keys, A., Anderson, J. T., Aresu, M., Björck, G., Brock, J. F., Bronte-Stewart, B., Fidanza, F., Keys, M. H., Malmros, H., Poppi, A., Postell, T., Swahn B., and del Vecchio, A., *J. clin. Invest.*, 1956, **35**, 1173.
29 —— and Buzina, R., *Circulation*, 1956, **14**, 479.
30 —— *J. Amer. med. Ass.*, 1957, **164**, 1912.
31 Kobernick, S. D., Niwayama, G., and Zuchlewski, A. C., *Proc. Soc. exp. Biol. (N.Y.)*, 1957, **96**, 623.
32 Kraus, H., Prudden, B., and Hirschhorn, K., *J. Amer. Geriat. Soc.*, 1956, **4**, 463.
33 Logan, W. P. D., *Lancet*, 1952, **1**, 758.
34 Luongo, E. P., *J. Amer. med. Ass.*, 1956, **162**, 1021.
35 Mann, G. V., Teel, K., Hayes, O., McNally, A., and Bruno, D., *New Engl. J. Med.*, 1955, **253**, 349.
36 Ministry of Agriculture, Fisheries and Food, Domestic Food Consumption and Expenditure. 1955.
37 Branwood, A. W., and Montgomery, G. L., *Scot. med. J.*, 1956, **1**, 367.
38 Morgan, A. D., *The Pathogenesis of Coronary Occlusion*. Blackwell Scientific Publ., Oxford. 1956.
39 Morris, J. N., *Lancet*, 1951, **1**, 1, 69.
40 —— *Uses of Epidemiology*. Livingstone, Edinburgh. 1957.
41 —— *Circulation*, 1958, **17**, 321.
42 —— and Dale, R. A., *Proc. roy. Soc. Med.*, 1955, **48**, 667.
43 —— Heady, J. A., Raffle, P. A. B., Roberts, C. G., and Parks, J. W., *Lancet*, 1953, **2**, 1053, 1111.
44 —— —— —— ibid., 1956, **2**, 569.
45 —— and Raffle, P. A. B., *Brit. J. industr. Med.*, 1954, **11**, 260.
46 Morrison, S. L., ibid., 1957, **14**, 130.
47 Muir, R., *Textbook of Pathology*, 6th ed. Ed. Cappel, D. F. Arnold, London. 1951.
48 Myasnikov, A. L., *Circulation*, 1958, **17**, 99.
49 Miall, W. E., and Oldham, P. D. (1958). *Clin. Sci.*, **17**, 409.
50 Orma, E. J., *Acta physiol. scand.*, 1957, Suppl. 142.
51 Orr, J. B., *Food, Health and Income*, Macmillan, London. 1936.
52 Osler, W., *Lancet*, 1910, **1**, 697.
53 Phipps, C., *J. Amer. med. Ass.*, 1936, **106**, 761.
54 Pickering, G. W., *High Blood Pressure*. Churchill, London. 1955.
55 Raab, W., *A.M.A. Arch. intern. Med.*, 1958, **101**, 194.
56 Registrar-General, *Decennial Supplement, England and Wales, 1931. Part IIA. Occupational Mortality*. H.M.S.O., London. 1938.
57 —— ibid., *1951. Part II. Occupational Mortality*. H.M.S.O., London. 1958.
58 —— *Classification of Occupations*, 1950.
59 Registrar-General, Scotland (1957).
60 Russell, D., *J. med. Wom. Fed.*, 1958, **40**, 4.
61 Scherf, D., and Golbey, M., *Amer. Heart J.*, 1954, **47**, 928.
62 Simonson, E., *Geriatrics*, 1957, **12**, 28.
63 Spain, D. M., and Bradess, V. A., *A.M.A. Arch. intern. Med.*, 1957, **100**, 228.
64 Stamler, J., *Neb. St. med. J.*, 1956, **41**, 75.
65 Gross, H., and Sternberg, W. H., *Arch. intern. Med.*, 1939, **64**, 249.
66 Thomas, A. J., Cotes, J. E., and Higgins, I. T. T., *Lancet*, 1956, **1**, 414.
67 Turnbull, H. M., *Quart. J. Med.*, 1915, **8**, 201.
68 Warnock, N. H., Clarkson, T. B., and Stevenson, R., *Circulat. Res.*, 1957, **5**, 478.
69 Yater, W. M., Welsh, P. P., Stapleton, J. F., and Clark, M. L., *Ann. intern. Med.*, 1951, **34**, 352.
70 Zoll, P. M., Wessler, S., and Schlesinger, M. J., *Circulation*, 1951, **4**, 797.

PREMATURITY AND "CEREBRAL PALSY"

BY

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That there is an association between prematurity and "cerebral palsy"* impressed the earliest students of this neurological condition (Little, 1862; Freud, 1897). Its nature has puzzled many; for some, like Brissaud (1894), the effect of prematurity is to cause a developmental anomaly of the pyramidal tracts; for others, like Collier (1924), the two conditions are parallel manifestations of an intrauterine abnormality causing both prematurity and primary antenatal degeneration of cerebral neurones.

Although data on prematurity are available in the collection of cases published by Little, it is largely in recent times that the association between prematurity and cerebral palsy has been put on a quantitative basis. Evans (1948), in 76 cases, and Asher and Schonell (1950), in 400 cases, found an incidence of prematurity of 39%, about eight times that in the normal population, while Lilienfeld and Parkhurst (1951), for 505 cases, give a figure of 22.2% with an incidence of prematurity in their control population (115,281) of 4.8%. It is to be noted that the controls used by Lilienfeld and Parkhurst were survivors at the end of the first month of life, those of Asher and Schonell were survivors at the end of the first year, and those of Evans were matched for age with his cerebral palsy cases. So that in these studies an attempt was made to overcome the error that would result from using figures referring to incidence of prematurity at birth due to the high mortality of premature infants (mainly in the neonatal period), particularly those of lower birth weight (Alm, 1953; Dunham, 1955).

A further idea of the importance of prematurity in cerebral palsy can be obtained from Evans's (1948) data, by considering the proportion of premature infants weighing 4½ lb. (2,040 g.) or less at birth. The relevant figures are: 21 such premature infants among 76 cerebral palsy cases and 1 among 50 controls (28% and 2% respectively). The figures given by Knobloch *et al.* (1956) further support this point. They found an incidence of "overt neurological defect" at 40 weeks of 12.3% in 57 premature babies weighing 1,500 g. or less, of 1.6% in 443 larger prematures, and of 0.6% in 492 full-term controls matched for race, season of birth, parity, hospital of birth, and socio-economic status.

Cerebral palsy is an aggregate of clinical syndromes with various origins, and so is prematurity. The causes of prematurity act on the foetus with varied intensity and at different developmental stages. Furthermore, the foetus prematurely delivered is exposed to extra risks during labour, and the premature newborn baby also faces numerous hazards.

Incidence of Prematurity in Cerebral Palsy

One might expect some types of cerebral palsy to be more strongly associated with prematurity than others. Freud (1897) and Brissaud (1894) correlated prematurity particularly with diplegia. The combined figures of Evans (1948) and Asher and Schonell (1950) show a significant difference in the incidence of prematurity between "non-rhesus athetoids" (29% of 74 cases) and "paraplegias and tetraplegias" (44% of 223 patients). The proportion of prematures among 104 cases of congenital hemiplegia was reported by Asher and Schonell as 30% and by Perlstein and Hood (1953) in their 222 cases as 12%.

A series of 93 cases of dystonic and choreo-athetoid cerebral palsy† was analysed (Polani, 1957, unpublished data). Of 28 cases with severe neonatal jaundice due to blood-group iso-immunization three were premature (11%); of 20 patients with a history of severe neonatal jaundice not associated with blood-group incompatibility 14 were premature (70%); and of 45 patients who did not have severe neonatal jaundice 16 were premature (35.5%). By contrast, in a group of 42 patients with cerebral spastic paraplegia/diplegia,‡ 59.9% were premature (Polani, 1957, unpublished data). Thus the association with prematurity seems high in cerebral palsy due to non-rhesus jaundice and in cerebral spastic paraplegia/diplegia.

The figures given by Ingram and Kerr (1954) confirm the striking association between cerebral spastic paraplegia/diplegia and prematurity (see Table). These figures suggest

Survivors, by Birth Weight, Edinburgh, 1948–52 (Ingram and Kerr, 1954)

Birth Weights	No. of Survivors	Diplegics/ Paraplegics Total No.	Incidence per 1,000
All weights	36,400	36*	1
Over 5½ lb. (2,500 g.)	35,143	23*	0·65
4–5½ lb. (1,800–2,500 g.)	1,017	2	1·96
Under 4 lb. (1,800 g.)	240	11	45·83

* Estimated on the basis of the period 1943–7 (33 cases in 35,866 children).

that, compared with full-term children, premature babies of high birth weight show a threefold increase in the incidence of cerebral spastic paraplegia/diplegia and those of lower birthweights a seventyfold increase. Thus among premature infants weighing under 4 lb. (1,800 g.) at birth the chance of cerebral spastic paraplegia or diplegia is apparently about 1 in 20.

If we accept Lilienfeld and Parkhurst's (1951) idea of a "continuum of reproductive wastage," with cerebral palsy as one link in a chain of unfavourable reactions, other elements of which are mental defect (Pasamanick and Lilienfeld, 1955b; Lilienfeld and Pasamanick, 1956), epilepsy (Lilienfeld and Pasamanick, 1954; Pasamanick and Lilienfeld, 1955a), behaviour disorder (Pasamanick, 1954; Rogers *et al.*, 1955, Pasamanick *et al.*, 1956), and foetal and neonatal death, we may observe even more subtle cerebral effects associated with prematurity. For example, the lowered intelligence quotient found by Douglas (1956) in his group of premature children, and confirmed by Dann *et al.* (1956), may represent more limited (or different) results of a harmful association between prematurity and brain function.

Causal Connexion

What could be the causal connexion in the association between prematurity and cerebral palsy? As stated, this association may manifest itself in different effects, depending on the different causes of prematurity, the different times in foetal development when they act, their different intensities, and the various stresses to which prematurity itself subjects

*This term is used here to mean a persisting qualitative motor disorder due to non-progressive damage of the encephalon occurring before the growth of the central nervous system is complete.

†In dystonic cerebral palsy abnormalities of muscle tone predominate, and the hypertonus, when present, is plastic in character (Denny-Brown, 1946). In choreo-athetoid cerebral palsy the outstanding motor abnormality is the presence of unwanted movements—dyskinesia of Perlstein (1952) and Balf and Ingram (1955).

‡Cerebral spastic paraplegia denotes a condition of lower-limb paralysis of cerebral origin, without notable functional involvement of the upper limbs. Patients with spastic diplegia have predominantly lower-limb and trunk involvement, and also upper-limb involvement, which, however, is less marked than that of the lower limbs. The difference between the two conditions may be essentially one of degree.

the developing organism. To deal with one example, prematurity may cause cerebral palsy (generally dystonic or choreo-athetoid cerebral palsy) through the mechanism of neonatal jaundice. Premature babies have a greater tendency to a rise in the serum-bilirubin level, presumably because of an inability of their livers to conjugate the liposoluble bilirubin (indirect-reacting bilirubin) with glucuronic acid and transform it into the water-soluble pigments I and II (direct bilirubin, bilirubin mono- and diglucuronide) (see Cole and Lathe, 1953; Billing *et al.*, 1957; Gray, 1957). For this reason, in a proportion of premature infants, even in the absence of increased haemolysis due to blood-group iso-immunization, the serum bilirubin will rise to dangerous levels and the liposoluble pigment cross the blood–brain barrier and produce kernicterus*.

If the breakdown of red cells is increased, as, for instance, when certain vitamin-K analogues are given in excess (Laurance, 1955; Crosse *et al.*, 1955; Allison, 1955), the extra production of bilirubin will increase the proportion of premature babies who get kernicteric damage. It has furthermore been shown by Diamond (1956) that the administration of sulphafurazole ("gantrisin") to premature babies may favour kernicteric damage without an excessive rise in serum bilirubin; Lathe (1957) has suggested that this is due to a lowering of the threshold of the blood–brain barrier. Kernicterus in a rabbit has been produced by this mechanism (Ernster *et al.*, 1957).

Anoxic and Mechanical Trauma

But prematurity may be responsible for cerebral palsy through other mechanisms. The premature baby is generally frail and his respiratory efficiency is often less than that of the full-term infant, with consequent possibilities of "anoxia." Furthermore, the lower the birthweight of premature infants (Calkins, 1955) the higher the incidence of breech delivery, which exposes the foetus and the newborn to added risks from mechanical or asphyxial injury, with consequent possibility of brain damage and so of cerebral palsy. Such mechanical or "anoxic" trauma would explain reasonably well some forms of cerebral palsy, such as double hemiplegia and "post-anoxic" choreo-athetoid and dystonic forms of the disorder.

Although, admittedly, anoxia can be selective in its action, the frequency of the association between cerebral spastic paraplegia and prematurity is more difficult to explain adequately on the grounds of a relatively indiscriminate and diffuse cerebral damage. The post-prematurity spastic paraplegia type of cerebral palsy is a striking clinical entity, striking for the symmetry of the neurological signs, for their distribution, for the relatively good intelligence of the patients, and for their comparative freedom from seizures; and all these features tend to militate against the idea of brain injury being responsible.

Possibility of a Development Mechanism

A developmental origin (Brissaud, 1894) seems a more logical explanation for the syndrome, and it might be reasonable to accept Collier's (1924) idea that the same factors which are responsible for the disturbed mother/foetus relationship, and so for prematurity, are also responsible for the disorder of brain development and so for cerebral spastic paraplegia. If this were so, the incidence of cerebral spastic paraplegia (and diplegia) might be expected to vary in groups of premature infants when the prematurity is due to different causes. If the disordered development were related to the cause of prematurity it would follow that the cerebral abnormality would be of prenatal origin. Prevention would be possible only if the causative factors were avoidable.

It should be made clear that when cerebral palsy cases are compared with a control population to assess the importance of obstetric factors in the aetiology of cerebral palsy (toxaemia of pregnancy, ante-partum haemorrhage, breech delivery, forceps delivery, breathing "difficulty," etc.) the control population generally contains a much lower proportion of premature children, so that what such comparisons reveal in the cerebral palsy population is the excess of obstetrical factors responsible for the prematurity though not necessarily for the cerebral palsy. Such comparisons would be more valid if the control population were matched for incidence of prematurity.

Few studies have separated prematurity into aetiological groups and correlated them with the frequency of cerebral palsy, thus trying to link *causes* of prematurity and cerebral palsy. Douglas's (1956) findings are worth noting in this context, though they do not refer to cerebral palsy but to mental ability of premature children. He examined a prospectively studied national sample of premature children aged 8 years and found a small group of them who made ". . . outstandingly poor scores in all tests—namely, those whose prematurity is unexplained either by obstetric abnormality" or by their genetic background. Lilienfeld and Parkhurst (1951) found a higher incidence of prematurity among those cases of cerebral palsy where complications of pregnancy and labour had not been present than among those where they had. They tried to explain this finding by suggesting a higher mortality rate among cerebral palsy premature infants with complications of pregnancy. Eastman and DeLeon (1955) have shown that in only one-third of their cerebral palsy cases associated with prematurity was there a complication of pregnancy that could have been responsible for the cerebral palsy through the mechanism of foetal anoxia. In two-thirds they concluded that the origin of cerebral palsy was in some way attributable to the prematurity itself.

It is possible to suggest mechanisms by which prematurity, by itself, is at times the operative factor in determining the paraplegia/diplegia type of cerebral palsy. The condition might be of post-natal origin, from failure of final structural and functional maturation of the brain, and it would then be the *degree* of prematurity rather than its cause that would be linked with the frequency of the condition. The figures of Ingram and Kerr (1954), given in the Table, stress the association between a greater degree of prematurity and a greater frequency of cerebral spastic paraplegia/diplegia.

A Matter for Conjecture

How this particular type of cerebral palsy could be produced by prematurity itself is a matter for conjecture. A possible explanation would be one that took into consideration the relatively anaerobic metabolism of the foetal nervous system, and its maturation, centre by centre, to the adult aerobic metabolism, apparently essential for the quick release of high energy presumably required for brain function. This has been demonstrated in the experimental animal by Himwich (1951) and his collaborators, and has been suggested in the human by the work of Racker (1942). It is a plausible conjecture that, possibly through interference with enzymic maturation or adaptation, premature birth deprives those parts of the nervous system which are at a crucial stage of anatomical development or functional maturation of the environment favourable to this development or maturation. The damaging factor may well not be anoxic, but rather hyperoxic, though even a hyperoxic insult may ultimately result in anoxic damage through interference with oxidative enzymes (Himwich, 1953; Dickens, 1946a, 1946b). Alternatively, brain structure and function may be damaged by a prolonged condition of absolute or relative hyperoxia, through alteration of the blood vessels of the differentiating cortex, much as can happen in the eyes of premature babies, with consequent retrolental fibroplasia.

It is perhaps relevant in this connexion to mention the work of Ashton *et al.* (1957), who poisoned the eyes of kittens with fluoride and iodoacetate and observed changes

*The present evidence is in favour of the cerebral damage being due to a direct action (Claireaux *et al.*, 1953; Ernster *et al.*, 1957).

similar to those resulting from exposure to high oxygen concentrations. They tentatively suggested that the mechanism at work was one of inhibition of glycolysis resulting in swelling of retinal tissue and subsequent vascular compression and obliteration (see also Graymore, 1958). By this technique they were able to produce a biochemical lesion owing to a particular vulnerability linked to a definite stage of functional development and maturation, and it is worth noting that similar changes could not be produced by them in the eyes of more adult cats. If the incidence of cerebral palsy (particularly cerebral spastic paraplegia/diplegia) were greater in babies stressed by high oxygen concentrations, the hyperoxic hypothesis would perhaps be more acceptable. Fuldner (1955) found an association between cerebral spastic paraplegia and retrolental fibroplasia. That the incidence of cerebral spastic paraplegia/diplegia in babies with retrolental fibroplasia is greater than would be expected has been shown by Ingram and Kerr (1954). However, they suggested that the cause of cerebral damage in their patients was abnormality of pregnancy and of labour, leading to post-natal asphyxia which necessitated oxygen therapy and in turn caused retrolental fibroplasia.

The above suggestion that premature birth may at times cause post-natal interference in development and maturation of critically maturing neurones is entirely hypothetical. It can be put to the test by experiments with high oxygen pressures in immature animals. The understanding of the delicate metabolic mechanisms involved can be furthered by detailed studies of the vascular, enzymic, histological, and functional maturation of the human brain, in continuation of the work done by Racker (1942) and Villee (1953). The main use of such a hypothesis is that it directs attention to possibilities of prevention.

Summary

The incidence of prematurity in various clinical types of cerebral palsy is reviewed. A particularly strong association is found with two neurological syndromes: dystonic/choreo-athetoid cerebral palsy following severe neonatal jaundice not due to blood-group incompatibility, and cerebral spastic paraplegia/diplegia. The possible mechanisms of this latter relationship are considered and a selective developmental origin for the neurological troubles is favoured tentatively. Because of the association between retrolental fibroplasia and cerebral spastic paraplegia/diplegia, and because of the clinical features of the cerebral spastic paraplegia syndrome without history of perinatal or postnatal troubles, a postnatal interference with development is the mechanism postulated for this clinical type of cerebral palsy.

The terminology on cerebral palsy used in this paper is based on the discussions of a group of workers interested in the subject at meetings of the Little Club. The help of those concerned is gratefully acknowledged.

REFERENCES

Allison, A. C. (1955). *Lancet*, **1**, 669.
Alm, I. (1953). *Acta paediat. (Uppsala)*, Suppl 94, p. 58.
Asher, Patria, and Schonell, F. Eleanor (1950). *Arch. Dis. Childh.*, **25**, 360.
Ashton, N., Graymore, C., and Pedler, C. (1957). *Brit. J. Ophthal.*, **41**, 449.
Balf, C. L., and Ingram, T. T. S. (1955). *Brit. med. J.*, **2**, 163.
Billing, Barbara H., Cole, P. G., and Lathe, G. H. (1957). *Biochem. J.*, **65**, 774.
Brissaud, E. (1894). *Sem. méd. (Paris)*, **14**, 89.
Calkins, L. A. (1955). *Amer. J. Obstet. Gynec.*, **69**, 977.
Claireaux, A. E., Cole, P. G., and Lathe, G. H. (1953). *Lancet*, **2**, 1226.
Cole, P. G., and Lathe, G. H. (1953). *J. clin. Path.*, **6**, 99
Collier, J. (1924). *Brain*, **47**, 1.
Crosse, V. M., Meyer, T. C., and Gerrard, J. W. (1955). *Arch. Dis. Childh.*, **30**, 501.
Dann, M., Levine, S. Z., and New, E. V. (1956). Communication No. 232, VIII International Congress of Paediatrics, Copenhagen. Abstracts of Papers, p. 132.
Denny-Brown, D. (1946). *Diseases of the Basal Ganglia and Subthalamic Nuclei*. Oxford Univ. Press, New York.
Diamond, L. K. (1956). Communication No. 207, VIII International Congress of Paediatrics, Copenhagen. Abstract of Papers, p. 114.
Dickens, F. (1946a). *Biochem. J.*, **40**, 145.
—— (1946b). Ibid., **40**, 171.
Douglas, J. W. B. (1956). *Brit. med. J.*, **1**, 1210.
Dunham, Ethel C. (1955). *Premature Infants*, 2nd ed., p. 341. Cassell, London.
Eastman, N. J., and DeLeon, M. (1955). *Amer. J. Obstet. Gynec.*, **69**, 950.
Ernster, L., Herlin, L., and Zetterström, R. (1957). *Pediatrics*, **20**, 647.
Evans, P. R. (1948). *Arch. Dis. Childh.*, **23**, 213.
Freud, S. (1897). Die Infantile Cerebrallahmung. In H. Nothnagel's *Spezielle Pathologie und Therapie*, Band IX, Thiel II, Abtheilung II. Hölder, Vienna.
Fuldner, R. V. (1955). *A.M.A. Arch. Neurol. Psychiat.*, **74**, 267.
Gray, C. H. (1957). *Brit. med. Bull.*, **13**, 94.
Graymore, C. (1958). *Brit. J. Ophthal.*, **42**, 348.
Himwich, H. E. (1941). *Brain Metabolism and Cerebral Disorders*, p. 125. Williams and Wilkins, Baltimore.
—— (1953). In *Prematurity, Congenital Malformation, and Birth Injury*, p. 73. Association for the Aid of Crippled Children, New York.
Ingram, T. T. S., and Kerr, J. D. (1954). *Arch. Dis. Childh.*, **29**, 282.
Knobloch, Hilda, Rider, R., Harper, P., and Pasamanick, B. (1956). *J. Amer. med. Ass.*, **161**, 581.
Lathe, G. H. (1957). *Proc. roy. Soc. Med.*, **50**, 713.
Laurance, B. (1955). *Lancet*, **1**, 819.
Lilienfeld, A. M., and Parkhurst, Elizabeth (1951). *Amer. J. Hyg.*, **53**, 262.
—— and Pasamanick, B. (1954). *J. Amer. med. Ass.*, **155**, 719.
—— —— (1956). *Amer. J. ment. Defic.*, **60**, 557.
Little, W. J. (1862). *Trans. obstet. Soc. Lond.*, **3**, 293.
Pasamanick, B. (1954). *Res. Publ. Ass. nerv. ment. Dis.*, **34**, 397.
—— and Lilienfeld, A. M. (1955a). *Neurology*, **5**, 77.
—— —— (1955b). *J. Amer. med. Ass.*, **159**, 155.
—— Rogers, M. E., and Lilienfeld, A. M. (1956). *Amer. J. Psychiat.*, **112**, 613.
Peristein, M. A. (1952). *J. Amer. med. Ass.*, **149**, 30.
—— and Hood, P. N. (1953). *Proceedings of the Annual Meeting of the American Academy of Cerebral Palsy*, Fort Worth, Texas, October 30, and 31, 1953.
Racker, E. (1942). *Fed. Proc.*, **1**, 69.
Rogers, M. E., Lilienfeld, A. M., and Pasamanick, B. (1955). *Acta psychiat. scand.*, Suppl. **102**, 1.
Villee, C. A. (1953). In *Prematurity, Congenital Malformation, and Birth Injury*, p. 78. Association for the Aid of Crippled Children, New York.

CORTICOTROPHIN AND STEROIDS IN THE DIAGNOSIS AND MANAGEMENT OF "OBSTRUCTIVE" JAUNDICE

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Jaundice due to hepatitis with prolonged bile retention (Eppinger, 1937; Watson and Hoffbauer, 1946) or occurring as a complication of therapy with chlorpromazine and other drugs (Hanger and Gutman, 1940; Hollister, 1957) may have clinical and biochemical features indistinguishable from that associated with extrahepatic biliary obstruction. Solem and Olsen (1953), aware that jaundice in patients with hepatitis often clears rapidly with steroid therapy (Ducci and Motlis, 1951), reported that the effect of a four to seven-day trial of corticotrophin (A.C.T.H.) therapy on the icteric index permitted a clear-cut distinction between extrahepatic obstructive jaundice, which was not significantly influenced, and hepatitis. However, later observations showed that the effect of corticotrophin or steroids in hepatitis was very variable (Sborov *et al.*, 1954) and that considerable reduction in serum bilirubin concentrations could follow use of the drugs in extrahepatic biliary obstruction, thus invalidating their application as a diagnostic test (Chalmers *et al.*, 1956; Katz *et al.*, 1957).

The subject has received only passing mention in this country (Shaldon and Sherlock, 1957; Summerskill, 1958), although the laparotomy indicated in extrahepatic obstruction may be unnecessary and hazardous in hepatitis. We therefore report the effect of corticotrophin and steroid drugs on serum bilirubin and alkaline

phosphatase levels in relation to ultimate diagnosis when applied exclusively to patients with "obstructive" jaundice of uncertain cause.

Material and Methods

Four male and eight female patients aged between 26 and 74 years (average 56) were studied (see Table). The clinical and biochemical findings consisted essentially of progressive jaundice, itching, and hepatomegaly, without fever, sudden prior deterioration in general health, or significant aetiological precedents. These were almost invariably associated with very high serum alkaline phosphatase levels; negative thymol turbidity and flocculation tests; the absence of occult blood or bile pigment from the stool and urobilinogen from the urine; and no relevant radiological abnormality on plain *x*-ray examination of the abdomen or by barium meal.

Five patients (Cases 1–5) had hepatitis, six (Cases 6–11) had extrahepatic biliary obstruction due to carcinoma later demonstrated at laparotomy, and an ampullary carcinoma was finally shown radiologically in one (Case 12). Jaundice had been present for periods of two weeks to three months and was accompanied by itching except in two cases (Nos. 6 and 7) with carcinoma. Case 3 had had a blood transfusion four months before the onset of jaundice, and a tooth was extracted three months previously in Case 5, but none gave a history of contact with hepatitis, recent injections, or drug consumption. Two patients (Cases 3 and 9) complained of vague prodromal symptoms, and one patient with hepatitis (Case 2) had had a cholecystectomy for gall-stones. One patient (Case 9) who had an operable ampullary carcinoma had profuse vascular "spiders," but none of the other patients showed cutaneous stigmata suggestive of liver-cell disease.

The serum bilirubin concentration was above 10 mg./100 ml. in all patients. The serum alkaline phosphatase level was elevated in all except Case 2, and the value was above 30 King–Armstrong units (normal <12 units) at the same stage in 10 patients. Flocculation tests were positive intermittently in Case 4 and negative in the remainder.

Serum bilirubin was estimated by a modification of the method of van den Bergh (1918), and serum alkaline phosphatase was measured by the method of King and Armstrong (1934). Corticotrophin or steroid drugs were given after at least two preliminary biochemical studies had been made during a control period of five or more days. The drugs were then given daily for five to eight days, after which time the biochemical investigations were repeated. In five patients longer courses of the drugs were given with continued biochemical control. Six patients received oral prednisone (60–50 mg. daily), five were given corticotrophin (60 units daily) by injection, two had oral cortisone (300–200 mg. daily), and one was treated with triamcinolone ("ledercort"; 9-alpha-fluoro-16-alpha-hydroxyprednisolone), 12 mg. daily. The drugs were used on 14 occasions, as two patients each had separate trials of corticotrophin and a steroid preparation.

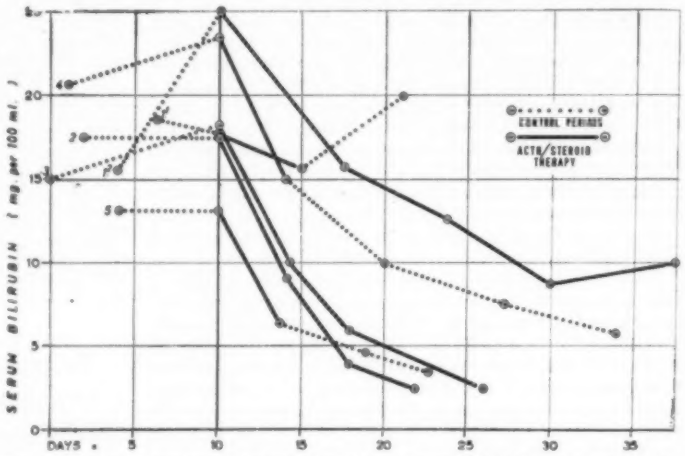

FIG. 1.—Effect of corticotrophin and steroids on serum bilirubin concentrations in hepatitis with obstructive features.

Results

Four of the five patients with hepatitis (Cases 2–5) showed a rapid and profound improvement in jaundice in response to corticotrophin or steroids after serum bilirubin levels had been unchanged or climbing in the control periods. Treatment was continued in Cases 2 and 3, with progressive clearing of the jaundice, whereas the biochemical improvement was slower in Cases 4 and 5, in which only short courses of the drugs were given (Fig. 1). The fall in serum bilirubin concentrations in these patients was between 8

Case Material and Response to Treatment with Corticotrophin and Steroids

Case No.	Sex and Age	Diagnosis	Duration of Jaundice Before Test	Drug and Duration	Serum Bilirubin (mg./100 ml.) Before	After	Change per Day	Serum Alkaline Phosphatase (K.A. Units) Before	After	Change per Day
1*†	F 64	Hepatitis (1)	6 weeks	Corticotrophin 60 u. daily ×5	17·5	16·0	−2%	31·5	18·5	−8%
		(2)	18 ,,	Triamcinolone 12 mg. daily ×7	25·0	16·0	−5%	88·5	73·0	−2%
2*	F 56	,,	4 ,,	Prednisone 60 mg. daily ×8	17·5	4·0	−9%	12·0	13·1	+1%
3*	M 63	,,	4 ,,	Cortisone 300 mg. daily ×7	18·0	6·0	−10%	28·5	22·0	−3%
4	F 48	,,	5 ,,	Prednisone 40 mg. daily ×4	23·5	15·5	−8%	—	—	—
5	F 26	,,	4 ,,	Corticotrophin 60 u. daily ×4	12·8	6·4	−12%	40·0	28·0	−7%
				Mean	19·0	10·6	−8%	40·1	30·9	−4%
6	F 56	Ampullary carcinoma	2 weeks	Corticotrophin 60 u. daily ×5	12·5	10·0	−4%	57·0	45·5	−4%
7*	F 58	,, ,,	5 ,,	Prednisone 60 mg. daily ×5	11·0	15·0	+7%	—	—	—
8	F 52	Carcinoma of gall-bladder and bile ducts	3 ,,	Corticotrophin 60 u. daily ×5	16·0	10·0	−7%	28·0	24·0	−3%
9	M 52	Carcinoma of common bile duct (1)	2 ,,	Corticotrophin 60 u. daily ×7	15·0	9·0	−6%	63·0	20·5	−10%
		(2)	4 ,,	Prednisone 60 mg. daily ×7	24·0	12·5	−7%	21·8	16·1	−4%
10	F 74	Ampullary carcinoma	4 ,,	Prednisone 60 mg. daily ×5	20·0	25·0	+5%	67·5	62·5	−1%
11	M 63	,, ,,	3 ,,	Prednisone 50 mg. daily ×5	18·0	15·0	−3%	57·3	68·0	+4%
12	M 63	Ampullary carcinoma and portal cirrhosis (inactive)	3 months	Cortisone 200 mg. daily ×5	15·0	16·0	+1%	74·0	79·5	+1%
				Mean	16·4	14·0	−2%	51·2	45·1	−2%

* Patients receiving longer courses of drug in addition (see Figs. 1 and 2).

† Presumed to have hepatitis on the basis of a negative laparotomy and surgical cholangiography. However, nine months later, jaundice and itching continues and the possibility of a bile-duct carcinoma becomes increasingly likely.

and 12% a day (see Table). The other patient (Case 1) failed to respond to corticotrophin and had a less impressive reaction, which was not sustained, with steroid therapy (Fig. 1).

There was a slight decrease (Cases 6 and 11) or negligible increase (Cases 7, 10 and 11) in serum bilirubin levels in five patients with extrahepatic obstruction during the administration of corticotrophin or steroids. Case 8 showed a fall equivalent to 7% a day, but the level was declining in the control period and failed to rise after corticotrophin was stopped. Case 9 had particularly convincing responses to

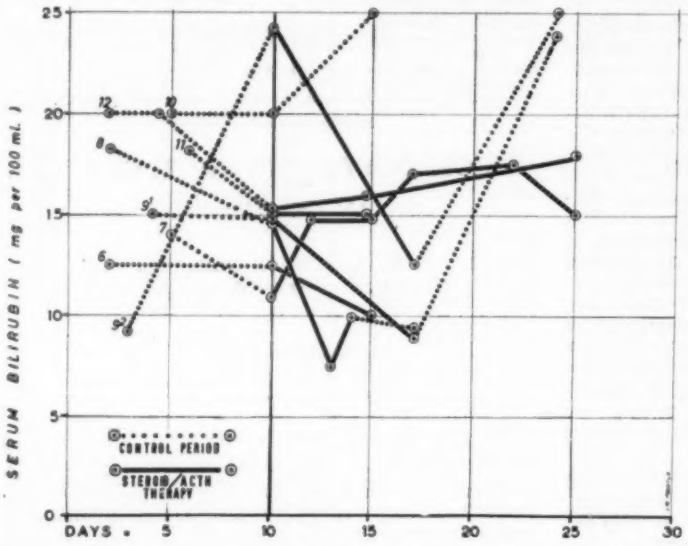

FIG. 2.—Effect of corticotrophin and steroids on serum bilirubin concentration in extrahepatic obstructive jaundice.

both corticotrophin (a fall of 6% a day) and prednisone (a fall of 7% a day), as there were sharp returns of the serum bilirubin concentration up to control levels as soon as the drugs were stopped (Fig. 2).

Changes in serum alkaline phosphatase concentrations were usually similar to those in the serum bilirubin levels, although less striking in degree (see Table). The level tended to fall during treatment in patients with hepatitis and extrahepatic obstruction but to a greater extent in the former group. Changes in serum bilirubin and alkaline phosphatase levels were occasionally disproportionate (Cases 1, 2, 10, and 11).

No apparent difference in response of the serum bilirubin and alkaline phosphatase levels was found in relation to the drug used (see Table) or to the doses prescribed. When a response occurred it took place immediately, and the duration of drug administration for longer than a period of four to five days was of importance only as a therapeutic measure in patients with hepatitis (Figs. 1 and 2).

Apart from fluid retention in Case 9 during corticotrophin administration, no toxic effect resulted from diagnostic use of the drugs. Case 1, however, had mental changes during the long-term administration of prednisone, and later, when still jaundiced, developed a duodenal ulcer while receiving triamcinolone.

Liver biopsy was performed for diagnostic purposes in four patients. Histological appearances of obstruction were found on three occasions, and these were non-specific in Cases 1 and 9, although the additional features of inflammatory cell infiltration of the lobules suggested hepatitis in Case 2. In Case 12, portal cirrhosis was found, without definite evidence of biliary obstruction, although it was subsequently proved that jaundice was due to obstruction from an ampullary carcinoma.

Discussion

These findings accord with earlier observations that corticotrophin and steroid compounds may influence the jaundice both of hepatitis and of extrahepatic obstruction, but they challenge the conclusion (Chalmers *et al.*, 1956) that the drugs have no application for the purpose of differential diagnosis between the two conditions. Four of five patients with intrahepatic obstructive jaundice due to hepatitis had reductions in serum bilirubin levels which exceeded any that occurred in patients with extrahepatic obstruction due to tumour. The "critical" figure in this series was a fall in the serum bilirubin level of 8% or more a day in a period of four to eight days, and review of earlier studies in patients with extrahepatic biliary obstruction shows that such a response to corticotrophin is very rare indeed in such cases (Chalmers *et al.*, 1956; Katz *et al.*, 1957). However, the practical importance of the procedure is the continued administration of the drugs to those who have shown some definite response to the initial test, as sustained improvement permits a confident diagnosis of hepatitis. Corticotrophin or steroid therapy is the treatment of choice for such patients (Johnson and Doenges, 1956), although histological improvement lags behind apparent clinical and biochemical recovery (Shalden and Sherlock, 1957).

Failure to improve with treatment does not exclude hepatitis, and the variable response of patients with hepatitis to corticotrophin or steroids is unexplained. In virus hepatitis, a proportion of patients may present with variable clinical, biochemical, or histological features of obstruction, and these sometimes dominate the picture. Six patients with such "cholangiolitic" findings responded to corticotrophin very much better than the remainder of 49 cases of hepatitis treated by Sborov *et al.* (1954); and Johnson and Doenges (1956) also commented on the prompt improvement after corticotrophin in two cases of hepatitis with obstructive features.

This susceptibility of patients with hepatitis and intrahepatic bile retention to respond to corticotrophin probably explains the success of corticotrophin and steroids as a diagnostic test for obstructive jaundice in this series, in contrast to the overlap in effect reported by Chalmers *et al.* (1956) when patients with "classical" hepatitis were compared with those with extrahepatic obstruction. Certain drugs, notably chlorpromazine, may produce identical features of prolonged intrahepatic bile retention, but this will be evident on direct questioning of the patient or his practitioner. Reports of the effect of corticotrophin or steroids on the jaundice of such cases are conflicting (Hollister, 1957), and insufficient data are at present available. In addition, it is likely that other agents, at present unrecognized, may produce the syndrome of intrahepatic bile retention, and in only two of the five patients reported here could any accepted aetiological factor be incriminated. The poor response to steroids and the atypical nine months course in Case 1 could be explained on this basis.

The mode of action of corticotrophin and steroids in lowering serum bilirubin concentrations in some patients with extrahepatic obstructive jaundice is uncertain. The original conception of a choleretic action (Patterson *et al.*, 1954) would seem to be invalidated by the observation that prednisone or cortisone causes no increase in faecal urobilinogen and bilirubin, despite reduction of serum and urinary bilirubin levels (Katz *et al.*, 1957). Occasionally, as could have happened in Case 8, treatment may coincide with spontaneous improvement in jaundice and the degree of

bilirubin excretion. The decreases in serum bilirubin concentrations during treatment in Case 9 cannot be attributed to this, and delay in red cell or haemoglobin breakdown due to steroids (Katz *et al.*, 1957) seems unlikely to explain such great reductions. Alternatively, deviation of haemoglobin metabolism to compounds which do not react with the diazo reagent, or increased storage of bilirubin in the reticulo-endothelial system and other tissues, might be responsible, but the coincident decreases in this study in serum levels of alkaline phosphatase, which is thought to be eliminated mainly in the bile, are more compatible with increased excretory activity.

The usefulness of corticotrophin and steroids in distinguishing between intrahepatic and extrahepatic jaundice has encouraged us to incorporate the test in the routine investigation of obstructive jaundice of uncertain cause. After two weeks, in which time standard investigations (stool occult blood, haematology, barium meal, liver-function tests) have been done, a five-day trial of corticotrophin or steroids on the serum bilirubin level is performed if the diagnosis remains in doubt. Oral prednisone (20 mg. t.d.s.) may be the drug of choice. It reaches the liver direct in portal blood, and corticotrophin has the disadvantage of variable potency due to batch differences. An apparent response to this measure is followed by continued treatment. In patients who fail to respond and in whom there is no haematological contraindication, liver biopsy can be performed with less hazard than laparotomy in the jaundiced patient, and its interpretation in obstructive jaundice was well reviewed by Johnson and Doenges (1956).

Unfortunately, cases which are equivocal from clinical and biochemical standpoints often have non-specific histological findings. However, dilatation of large intrahepatic bile ducts and bile extravasation suggest extrahepatic obstruction, while, as in Case 2, evidence of liver-cell damage and cellular infiltration indicates hepatitis. In addition, cirrhosis or another unsuspected lesion may be demonstrated, as in Case 12. If the diagnosis is still in doubt, laparotomy with arrangements for cholangiography must be considered to resolve the doubts of both doctor and patient. Obstructive jaundice is not harmful (Atkinson *et al.*, 1956), and it is reasonable to wait eight weeks for possible improvement, as operation is poorly tolerated by patients with hepatitis (Sherlock *et al.*, 1954). Sometimes, as in Case 1 (who was jaundiced for nine months), laparotomy appears inevitable in a patient subsequently shown to have hepatitis, but the relative absence of liver-cell damage on clinical, biochemical, and histological investigation probably allows these patients to withstand operation better than others with hepatitis.

Summary

In 12 patients with obstructive jaundice of uncertain cause, the effect of a five-day trial of steroid or corticotrophin therapy was of great value in reducing serum bilirubin levels and in differentiating between intrahepatic obstruction due to hepatitis and extrahepatic obstruction. Serum alkaline phosphatase concentrations also fell during treatment, although to a less extent, thus suggesting that the reduction of jaundice caused by corticotrophin or steroid drugs was due to increased bile excretion. The drugs acted immediately and no difference was apparent between corticotrophin and steroids.

The place of these drugs and other measures in the diagnosis and management of obstructive jaundice is discussed.

We are grateful to the consultant staff of the Central Middlesex Hospital for permission to study these patients and to Dr. G. Discombe and Miss Mavis Smith for the biochemical results.

REFERENCES

Atkinson, M., Nordin, B. E. C., and Sherlock, S. (1956). *Quart. J. Med.*, **25**, 299.
van den Bergh, A. A. H. (1918). *Der Gallenfarbstoff im Blute*. Barth, Leipzig.
Chalmers, T. C., Gill, R. J., Jernigan, T. P., Svec, F. A., Jordan, R. S., Waldstein, S. S., and Knowlton, M. (1956). *Gastroenterology*, **30**, 894.
Ducci, H., and Motlis, J. (1951). *Rev. méd. Chile*, **79**, 590.
Eppinger, H. (1937). *Die Leberkrankheiten*. Springer, Vienna.
Hanger, F. M., and Gutman, A. B. (1940). *J. Amer. med. Ass.*, **115**, 263.
Hollister, L. E. (1957). *Amer. J. Med.*, **23**, 870
Johnson, H. C., and Doenges, J. P. (1956). *Ann. intern. Med.*, **44**, 589.
Katz, R., Ducci, H., and Alessandri, H. (1957). *J. clin. Invest.*, **36**, 1370.
King, E. J., and Armstrong, A. R. (1934). *Canad. med. Ass. J.*, **31**, 376.
Patterson, P. R., Dingman, J. F., Shwachman, H., and Thorn, G. W. (1954). *New. Engl. J. Med.*, **251**, 502.
Sborov, V. M., Giges, B., Plough, I. C., and Mandel, W. (1954). *J. Lab. clin. Med.*, **43**, 48.
Shaldon, S., and Sherlock, S. (1957). *Brit. med. J.*, **2**, 734.
Sherlock, S., Summerskill, W. H. J., White, L. P., and Phear, E. A. (1954). *Lancet*, **2**, 453.
Solem, J. H., and Olsen, A. (1953). *Acta med. scand.*, **146**, 281.
Summerskill, W. H. J. (1958). *Proc. roy. Soc. Med.*, **51**, 363.
Watson, C. J., and Hoffbauer, F. W. (1946). *Ann. intern. Med.*, **25**, 195.

THROMBOCYTOPENIC PURPURA DUE TO QUINIDINE

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The fundamental observations on drug-induced thrombocytopenia were made by Ackroyd (1949a, 1949b, 1951, 1954) in his classical work on "sedormid" purpura. He showed that the drug caused agglutination and lysis of the patient's platelets *in vitro*, and that the addition of the drug to the patient's blood *in vitro* inhibited clot retraction.

We describe below a simple method for showing platelet agglutination. This method enables the investigator to obtain suspensions of platelets which have no tendency to spontaneous clumping. Stress is laid on the clinical features of quinidine purpura and the practical conclusions to be drawn from them.

Case Report

On December 31, 1957, a man aged 50 was admitted to Hadassah Hospital because of haematuria and purpura. He looked seriously ill. There were widespread petechiae, and blood-filled blisters were seen in the mouth and on the tongue. The urine had the appearance of blood. The blood pressure was 170/100. The blood count showed haemoglobin, 69%; erythrocytes, 3,500,000; leucocytes, 10,000 (neutrophils 59%, eosinophils 2%, monocytes 2%, lymphocytes, 37%). No platelets were seen; bleeding-time was 2 minutes; coagulation time 2 minutes, and prothrombin 58%. The urine showed many red cells. The tourniquet test was strongly positive. Prednisone, 60 mg. a day, was given. By his fourth day in hospital the urine was clear, the platelet count had risen to 25,000, and he was feeling much better. By the seventh day the platelets had risen to 100,000; two days later they numbered 240,000.

A detailed history revealed that the patient had had a myocardial infarction two years previously. In July, 1957, he was given quinidine because of palpitations; he took four 0.2 g. tablets. A month later he took another tablet. Two days before admission he felt palpitations and took two tablets, one at midday and one in the evening (0.4 g.). That night he had a severe rigor and his temperature rose to 39° C. (102.2° F.). Next day he felt weak and noticed a rash on his hands. On the following day blood appeared in his urine and he was sent to hospital. He had taken 1.4 g. of quinidine at intervals, over a period of six months.

In the third hospital week—that is, when the patient's blood picture had become entirely normal and the prednisone treatment had been stopped—the following tests were carried out:

Clot Retraction Test, Qualitative Method

This test was done in the ward as follows: solutions (in normal saline) of quinidine sulphate 1:2,000 and quinine hydrochloride 1:2,000 were procured. Three standard laboratory test-tubes were taken; to the first was added 0.2 ml. of the quinine solution, to the second 0.2 ml. of the quinidine solution, and to the third 0.2 ml. of normal saline. Blood was taken from the patient by venepuncture, using a ward syringe. To each tube was added 2 ml. of blood. The tubes were inverted four times. They were kept at room temperature and examined after 4 and 24 hours. If free serum was seen the test was taken as negative; if no free serum could be seen it was regarded as positive. In this way quinidine repeatedly gave positive reactions, while quinine and saline always gave negative reactions (Fig. 1). Quinidine gave negative results when tested similarly with the blood of 10 other patients.

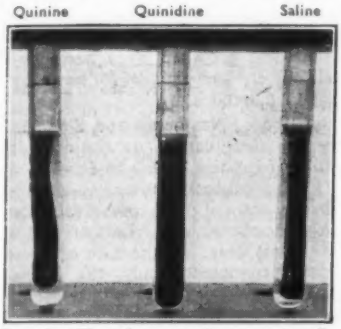

FIG. 1.—The clot-retraction test (qualitative method) as performed in the ward. The two outside tubes (quinine and saline) show negative results; the centre tube (quinidine) shows a positive result. In this photograph the test was done with Linzenmeier blood sedimentation tubes.

FIG. 2.—The thrombocyte-rich plasma of the patient after incubation with quinidine solution at 37° C. for one hour, showing agglutination of platelets (+++).

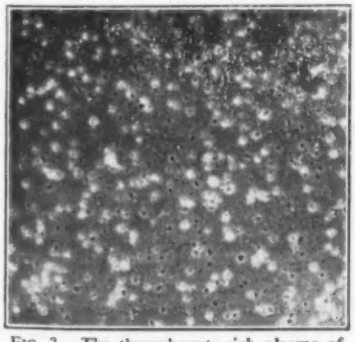

FIG. 3.—The thrombocyte-rich plasma of the patient with saline (control), showing complete absence of agglutination. Photographs of Figs. 2 and 3 were taken with the phase contrast microscope. (×400.)

The reliability of this simple procedure is stressed, since it enables the clinician to make the diagnosis in the ward. This test, as performed above, was still positive 10 weeks after the patient's admission; a further test four weeks later was negative. These results were confirmed in the laboratory, using the quantitative method.

Patch Test.—This was carried out according to the method of Freedman, Brody, and Barr (1956). The results were negative.

Thrombocyte Agglutination Test

The anticoagulant was Na_2 "sequestrene" 5% at *p*H 7.2 (corrected with NaOH). Glassware was siliconized with "siliclad." Drug solutions were made up as follows in normal saline: quinidine sulphate, 2 and 20 mg., quinine hydrochloride 2 and 20 mg., phenobarbitone 2 and 20 mg. per 100 ml. A siliconized bacteriological test-tube (5 cm. long with outside diameter 9 mm.) was marked with wax pencil at the 1-ml. level; 0.1 ml. of anticoagulant was added. After warming the hand a deep finger puncture was made. When the blood was flowing freely it was collected straight into the tube up to the mark and well mixed with the anticoagulant; 1 ml. of blood was usually enough. The tube was then centrifuged at room temperature at 800–1,000 r.p.m. for three to five minutes. The upper layer of thrombocyte-rich plasma was removed with a siliconized pipette and transferred to a small siliconized test-tube, which was tapped gently to secure even spread of the platelets. This thrombocyte-rich plasma was distributed into small siliconized test-tubes, two drops in each tube. To each tube was added one drop (of the same size) of one of the drug solutions under test. The mixtures were incubated for one hour in a water-bath at 37° C. The tubes were removed and, using a siliconized pipette, a small drop was placed on a siliconized slide, covered with a siliconized coverglass, and examined microscopically. Incubation for a further hour caused the agglutination to be even more marked; platelet flocculation could then be seen with the naked eye.

Results.—This test, and the clot-retraction test, were performed on the patient's blood in the third hospital week, and repeated once a week for eight weeks. Tests with the controls were done twice. The results were graded as follows:

+++, Complete agglutination into large clumps with no free platelets (as in Fig. 2).

++, Agglutination into smaller groups with free platelets to be seen.

+, Agglutination into very small groups; from 2 to 3 agglutinates visible in every field.

−, No tendency to agglutinate whatsoever. (As in Fig. 3.)

	Quinidine		Quinine		Phenobarb.		Saline
	2 Mg./100 ml.	20 Mg./100 ml.	2 Mg./100 ml.	20 Mg./100 ml.	2 Mg./100 ml.	20 Mg./100 ml.	
Patient	+++	+++	−	−	−	−	−
20 controls	−	−	−	−	−	−	−
6 patients on quinidine	−	−	−	−	−	−	−
Patient's daughter	−	−	−	−	−	−	−

Follow-up: fourteen weeks after admission the patient's platelet-rich plasma was examined again with quinidine; result was ++. At examination seven months after admission the result was +.

Clot Retraction Test, Quantitative Method

In this test the drugs and glassware were as above. 0.1 ml. of the drug solution was mixed with 0.9 ml. of the patient's blood, taken as above. The test-tubes were incubated for three hours at 37° C. Readings were made according to the formula:

$$\frac{\text{serum expressed, in ml.}}{\text{whole blood in ml.}} \times 100$$

Results are shown in the following Table.

	Quinidine 20 Mg./100 ml.	Quinine 20 Mg./100 ml.	Phenobarb. 20 Mg./100 ml.	Saline
Patient	0	52–56	52–56	52–56
20 controls	48–60	48–60	48–60	48–60
6 patients on quinidine	52–58	52–58	52–58	52–58
Patient's daughter	51	53	53	51

Follow-up: The test was repeated on the patient's blood 14 weeks and seven months after admission; clot retraction

in the presence of quinidine showed no difference from the saline control on both occasions.

Controls.—The controls for both tests were 20 patients and medical personnel of both sexes and various age groups who had never received quinidine. We also tested six patients who had regularly been receiving quinidine for periods varying from a month to a year. The blood of the patient's daughter was also examined.

Other Laboratory Procedures

In order to eliminate the possibility of idiopathic thrombocytopenic purpura due to a platelet panagglutinin in the patient's serum, the following procedure was carried out.

Samples of platelet-rich plasma from two normal persons, of the same blood group as the patient, were prepared as above. Two drops of the patient's serum (after inactivation for 30 minutes at 56° C.) were added to one drop of normal platelet-rich plasma, mixed and incubated for one hour, one sample at 4° C. and another at 37° C. Controls were: physiological saline and serum from two blood-compatible normal persons in place of the patient's serum. Thus, samples of platelet-rich plasma from two normal persons were tested with the patient's serum, the serum of two normal persons, and with saline. No agglutination was observed.

In order to find evidence of a factor in the patient's serum capable of agglutinating normal platelets in the presence of quinidine, the above procedure was repeated with the addition of one drop of quinidine solution (2 mg. per 100 ml.) to each mixture. Control tests were done simultaneously without quinidine. No agglutination was observed. This finding is commented upon below.

(These procedures were carried out in the third and fourth weeks following admission.)

Discussion

Dose of Quinidine

Purpura may appear at any time in any patient taking quinidine. Thus a patient may take quinidine for years, either continuously or intermittently, when suddenly purpura appears (Freedman *et al.*, 1956; Bigelow and Desforges, 1952). Sensitization may develop during a patient's first course of quinidine; in such cases there is a "lag" period before the onset of purpura; this period may be as short as five days (Collins, 1950). Some of the reported cases resemble our case, in which there is a definite history of a sensitizing dose, followed after an interval by the precipitating dose.

Patients suffering from quinidine purpura vary considerably in their sensitivity to the drug. This is readily seen in the summary compiled by Bolton and Dameshek (1956), in which are tabulated the results of the test doses given in the reported cases. Thus as little as 15 mg. caused the platelet count to drop to 5,000 with bleeding in one case, whilst in another case 0.2 g. caused the platelets to fall to 90,000, no bleeding taking place. The sensitivity of the individual patient also does not remain constant. This is exemplified in the case of Moodie (1950): here a test dose of 0.2 g. a day led to purpura after four days, but later on purpura appeared after a total of only 64 mg. had been administered during four days.

Since the sensitivity varies from patient to patient, and since the sensitivity varies in the same patient from time to time, it is impossible to fix an "optimal" test dose in any given case; by "optimal" is meant a dose which causes a drop in the platelet count large enough to be convincing but which does not cause bleeding. We believe that it is ethically wrong to give a test dose, because its outcome can never be predicted.

Although there is no definite correlation between the amount of quinidine ingested and the extent of the bleeding which it provokes, we stress that in the fatal case reported by Bourne and O'Sullivan (1957) the patient went on taking 0.96 g. of quinidine daily for four days after the onset of purpura. Death was due to cerebral haemorrhage. It follows that a patient should stop taking the drug at the very first signs of thrombocytopenia; it is of practical importance to know what these signs are.

Prodromal Symptoms

In our case there appeared to be a definite prodromal stage; after having taken two tablets of quinidine, the patient had a severe rigor during the night and his temperature rose to 39° C. Several authors describe similar features. Siegal and Horn (1950) reported fever after a test dose. Hirsch and Dameshek (1950) described a case in which gum bleeding and purpura were preceded by a chill and a feverish sensation. In Case 2 of Bolton and Dameshek (1956) the bleeding episode was preceded by a period of a week marked by chills, fever, and fatigue followed by nausea, abdominal pain, and diarrhoea.

Other symptoms are described. Nussbaum and Shulman (1952) described lethargy and somnolence. In the case of Collins (1950) lethargy followed a test dose. In Case 4 of Bolton and Dameshek (1956) weakness, nausea, and tiredness are mentioned. In the case of Norcross (1950) the illness began with coma and convulsions. Larson (1953) mentioned headache after a test dose. In the case of Breu and Zollner (1940), which terminated fatally, the illness started with anaphylactic shock and urticaria. Other symptoms mentioned in the case reports are itching, feeling uncomfortable, and pains in the limbs.

It is impossible to assess in what proportion of cases the purpura is preceded by prodromal symptoms, since some authors omit to state how the patient felt before the bleeding started. Barkham and Tocantins (1954) described a case without such symptoms.

It may be concluded that in an appreciable proportion of cases the bleeding episode is preceded by various symptoms, the main ones being fever, chills, weakness, lethargy, nausea, and headache. It may be noted that the prodromal symptoms of quinidine purpura share certain features with "cinchonism" (as described by Goodman and Gilman (1955)), such as nausea, headache, and fever.

The Haemorrhagic Episode

The bleeding may start in an atypical fashion. Our patient noticed black spots on his tongue, but their importance was understood only next day. In the case of Nussbaum and Shulman (1952) there occurred gum bleeding, which at the time was attributed to local causes. Local causes could easily be blamed for epistaxis or for uterine bleeding. Bleeding of all kinds and in all grades of severity have been described, including melaena, cerebral haemorrhage, haemoptysis, and haematuria. In the great majority of cases a purpuric skin rash is present.

It is worth noting that the best-known complication of quinidine treatment—embolism after reversion from atrial fibrillation to sinus rhythm—might be confused with the results of haemorrhage due to thrombocytopenia. For example, either of these complications might be the cause of haemoptysis during quinidine treatment. Should haematuria or hemiplegia appear the same differential diagnosis must be considered.

Duration of the Haemorrhagic Episode

Our patient was seriously ill on admission. His condition rapidly improved: seven days after his taking the quinidine the haematuria had ceased and the purpura was beginning to fade; return of the platelet count to normal levels took another four days. All the case reports of quinidine purpura show the same picture—that is, a haemorrhagic state which lasts from one to seven days after stopping the drug, full haematological remission usually coming some days later. Likewise, this same pattern is reported to be usually seen in cases of sedormid purpura. This "seven-day pattern" of thrombocytopenic purpura, characterized by cessation of bleeding within a week of stopping the drug, seems to be the typical result of the action of a rapidly eliminated factor whose primary effect is the destruction of

thrombocytes in the peripheral blood. Many reports of drug purpura in the literature conform to this "seven-day pattern." As examples may be cited the following cases: butobarbitone (Young, 1957), quinine (Steinkamp *et al.*, 1955), digitoxin (Berger, 1952), "mapharsen" ("mapharside," oxophenarsine hydrochloride) (Schwartz and VonderHeide, 1945). However, the clinical pattern cannot be taken as the only criterion in classifying the drug purpuras; it is merely suggestive. It may be postulated that the purpuras due to quinidine, quinine, and sedormid form a clinico-pathological entity.

To this group may be added other drugs if they conform to the following criteria: (*a*) The clinical picture should be typical, with cessation of bleeding within a week of stopping the drug, full haematological remission coming some days afterwards. (*b*) The primary action of the drug is platelet destruction in the peripheral blood. This may be assumed when thrombocytopenia follows within a few hours of giving the drug; absence of megakaryocyte aplasia in the bone marrow tends to confirm this. (*c*) Thrombocyte agglutination should be demonstrable in the presence of the drug *in vitro*. This should be confirmed by the inhibition of clot retraction in the presence of the drug.

Practical Considerations

The physician using quinidine will wish to know how common quinidine purpura is, and what should be done about it. In 1941 Broch described the first undoubted case: by 1956 Bolton and Dameshek were able to list 28 cases. If we add our case, the fatal case of Bourne and O'Sullivan (1957), and the four cases of Freedman *et al.* (1956), at least 34 cases are on record. The last-mentioned authors comment on the fact that they diagnosed their four cases during a period of seven months at one hospital. The condition is not common, but it is not merely of academic interest.

It is pointless to do daily platelet counts during the administration of quinidine, since the drop can occur suddenly at any time. It is the usual practice to give a test dose of one tablet before starting a course of quinidine; two to three hours later the treatment is begun if there are no untoward effects. We make the suggestion that if any suspicious symptoms arise a tourniquet test should be performed and, if possible, a platelet count done before proceeding. The physician prescribing quinidine should be alert for the prodromal symptoms of thrombocytopenia, described previously; the similarity of these symptoms to those of cinchonism must not be ignored. The appearance of constitutional symptoms calls for the immediate cessation of the drug, which must not be resumed until a platelet count is done. As many of the recorded cases of quinidine purpura were in patients who had been taking the drug at home with little or no supervision, it is important to impress on domiciliary patients to stop the drug and seek medical advice on the appearance of constitutional symptoms, a rash, or bleeding.

Serological Findings

The addition of quinidine to the patient's platelet-rich plasma caused the platelets to clump into large discrete masses. No lysis of platelets occurred; this agrees with Ackroyd's (1951) observation that lysis appears only in the presence of complement. We used sequestrene as anticoagulant, making use of its anticomplementary effect (Bolton, 1956), so as to prevent platelet lysis and thus simplifying the reading of the results.

In his studies on sedormid purpura, Ackroyd (1949a, 1949b) showed that there is a factor in the serum of sensitized patients, which, when added to the platelets of normal persons, causes agglutination in the presence of the drug. He concluded (Ackroyd, 1954) that sedormid unites with platelets to form an antigen which reacts with the factor in the serum. A similar factor in the serum of patients with quinidine purpura has been demonstrated by Bolton and Young (1953), Weisfuse, Spear and Sass (1954), and Bolton and Dameshek (1956); they were able to obtain agglutination of normal platelets on the addition of the patient's serum and quinidine. Bigelow and Desforges (1952) had inconsistent results, as they found the factor in plasma but not in serum. However, Barkham and Tocantins (1954) were unable to find such a factor in the serum of their patient. We, too, were not successful in demonstrating the presence of a serum factor. Apparently these inconsistencies are due to variations in technique, such as the choice of anticoagulant and the period and temperature of incubation.

However, we wish to put forward for consideration the following theoretical possibility: that the serological process is a direct antigen–antibody reaction between quinidine and sensitized platelets. It might then be postulated that changes in the platelets *in vitro* due to blood coagulation or to centrifugation could detach the factor from the platelets, and this could account for its presence in the serum. The extraordinary rapidity of action of quinidine in cases of sensitivity seems to support the idea of a direct reaction.

Summary

A case of quinidine purpura is described. It is shown that the diagnosis can be made in the ward by a simplified version of the clot-retraction test.

A simplified method for demonstrating platelet agglutination is described.

The prodromal symptoms of quinidine purpura are described and their importance is stressed.

It is shown that many of the drug-induced thrombocytopenias conform to a definite clinical pattern, and certain criteria are proposed for classification.

We are grateful to Dr. W. N. Wolff and Professor F. Rappaport for their help and encouragement. Our thanks are due to the patient for his willing co-operation.

References

Ackroyd, J. F. (1949a). *Clin. Sci.*, **7**, 249.
—— (1949b). Ibid. **8**, 235, 269.
—— (1951). Ibid., **10**, 185.
—— (1954). Ibid., **13**, 409.
Barkham, P., and Tocantins, L. M. (1954). *Blood*, **9**, 134.
Berger, H. (1952). *J. Amer. med. Ass.*, **148**, 282.
Bigelow, F. S., and Desforges, J. F. (1952). *Amer. J. med. Sci.*, **224**, 274.
Bolton, F. G. (1956). *Blood*, **11**, 547.
—— and Dameshek, W. (1956). Ibid., **11**, 527.
—— and Young, R. V. (1953). *J. clin. Path.*, **6**, 320.
Bourne, S., and O'Sullivan, D. J. (1957). *Brit. med. J.*, **1**, 1046.
Breu, W., and Zollner, S. (1940). *Wien. klin. Wschr.*, **53**, 524.
Broch, O. J. (1941). *Nord Med.*, **10**, 1542. Cited by Bolton and Dameshek (1956).
Collins, D. C. (1950). *Circulation*, **2**, 438.
Freedman, A. L., Brody, E. A., and Barr, P. S. (1956). *J. Lab. clin. Med.*, **48**, 205.
Goodman, L. S., and Gilman, A. (1955). *The Pharmacological Basis of Therapeutics*, 2nd ed. Macmillan, New York.
Hirsch, E. O., and Dameshek, W. (1950). *Amer. J. Med.*, **9**, 828.
Larson, R. K. (1953). *Blood*, **8**, 16.
Moodie, G. (1950). *Brit. med. J.*, **2**, 553.
Norcross, J. W. (1950). *New Engl. J. Med.*, **242**, 53.
Nussbaum, H. E., and Shulman, M. W. (1952). *Ann. intern. Med.*, **37**, 190.
Schwartz, M., and VonderHeide, E. C. (1945). *J. Amer. med. Ass.*, **128**, 657.
Siegal, S., and Horn, H. (1950). *Amer. Heart J.*, **39**, 302.
Steinkamp, R., Moore, C. V., and Doubek, W. G. (1955). *J. Lab. clin. Med.*, **45**, 18.
Weisfuse, L., Spear, P. W., and Sass, M. (1954). *Amer. J. Med.*, **17**, 414.
Young, F. (1957) *Brit. med. J.*, **2**, 919.

A memorandum on the care of epileptics has been prepared for the Central Health Services Council by the Standing Medical Advisory Committee and is to be sent to all general practitioners in the National Health Service. Concentrating on the medical and social aspects of epilepsy, the memorandum offers advice on the "management" of epileptics, and on their training and employment. There are paragraphs about the welfare services available to them, about epileptic colonies, and about the problems of marriage and having children. The memorandum states that there are about 180,000 epileptics in England and Wales: probably about 70% of cases occur before the age of 20 and 85% before the age of 25.

PLACE OF ROUTINE EXAMINATIONS IN PROMOTION OF HEALTH AMONG INDUSTRIAL EXECUTIVES*

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Although occupational medicine has been well recognized and well implemented in industry in the United States for a number of years, it is only during the past eight to ten years that the executive health phase of this programme has been stressed to any great extent. That industrial medicine has progressed rather rapidly during the past several years in the United States is shown by its recognition as a specialty under the American Board of Preventive Medicine, other subspecialties under this board being public health and aviation medicine.

Industrial Medical Programme

Management has recognized the value of a medical programme in industry, including an executive health programme. Ruffin (1957) has stated that "the health, wellbeing and morale of the men and women are among the most precious assets that we have in industry," and, in general, industry has accepted its measure of responsibility for the health and safety of its employees. Health maintenance programmes are of primary benefit to the employee, but they play their full share in keeping down the competitive costs, reducing operating expenses, and increasing efficiency. According to Proudfit (1957), the accumulated experience of companies that have fostered modern industrial medical programmes has made it plain that an investment in health is good business and that any manager who is required to operate without needed medical service or with expensive unsolved health problems in fiis employees knows it is bad business not to have available good medical counsel and service. He refers to a report furnished by the American Management Association in which it is concluded that, from data furnished by a number of industries with medical departments, there is a consistent profit of $3.50 to $5 for each dollar spent in the medical department.

Irvin (1952), as the result of comments obtained from a questionary submitted to executives who had undergone a periodic health check, concluded that health maintenance of key personnel was a sound financial investment and that the executive was very appreciative of the annual check-up on his physical status. Trickett (1952), in a survey of industry having executive health programmes in the San Francisco area, found that as a rule such a programme was of value. However, his study revealed that health problems of management employees were often overlooked, which seemed amazing, since direct or indirect financial loss can result from inadequate performance and also since executives are often careless of their own health.

There is considerable variance of opinions on whether or not the death rate among executives is greater than in similar age groups of individuals not occupying executive positions. However, we do know that disease incidence and trends have changed remarkably in the past several decades. There is less tuberculosis, and cases of communicable disease and pneumonia are fewer. The infant mortality is less and longevity is greatly extended. With increasing age there is less resistance to disease and consequently an increase in the number of degenerative diseases, with heart disease and malignancies being responsible for a large percentage of deaths in the older age groups. Since the executive is usually in the older age group he is more prone to acquire one of the degenerative diseases and therefore should be included in the health maintenance programme. Executive ability represents great worth to any industry, the potential value of the executive being variously estimated to be between $50,000 and $250,000, depending on how far down or up he is categorized on the management scale. The sudden death of or a serious disabling disease in a top executive has in some cases proved to be almost disastrous because of lack of continuity of management.

Objectives of a Health Programme

The objectives of an executive health programme are to provide health maintenance for the purpose of improving health, increasing efficiency, and prolonging life, protecting the company's investment, and ensuring continuity of management.

There are several guiding principles that are generally accepted. First, the programme must have the wholehearted support of management, since without such support it will fail. Second, it must be decided which groups are to be examined; in other words, will only the top executive groups be included in the programme or will it extend to the lower management groups down to and including the foremen? Third, how often will the periodic examination be given? This depends upon the number of personnel and equipment available and the economic cost. An annual examination is desirable if it can be accomplished within the provisions stated. An annual periodic examination after the age of 40 or 45, with a biennial examination up to that age, might be advisable. Fourth, should the examination be done by the company medical department or should the executive be referred to an outside hospital or clinic? There are arguments on both sides. It is generally believed that an examination by the company medical department is the better of the two plans, since it is more convenient, the medical director of the company is more familiar with the working conditions, follow-up medical procedures are easier to implement, and it is usually more economical. Fifth, the findings should be treated as confidential between the examinee and the examining physician. Sixth, those cases requiring definite medical care should be referred to ouside physicians.

Before discussing the routine examination, it is felt that a few words would be appropriate on the preplacement examination. In airline operation the preplacement examination for the pilot is very thorough, very exacting, and very selective. The examination is conducted not only on the basis of the applicant's present condition but also on the pilot's potential physical and mental condition twenty to thirty years in the future. On this basis a fair percentage of pilots are disqualified physically because of one or several minor defects which may in the future prove to be detrimental to his health. The disqualification rate of pilot applicants varies between 10 and 15%. On the other hand, the examination of the ground employee, including the potential executive, is not as exacting, since the condition of many of these individuals is acceptable for ground duty but not for pilot duty.

After the initial examination for employment, subsequent routine or periodic examinations are for the purpose of conserving or maintaining health. The main intent of this examination is to disclose disease processes in their incipiency so that corrective action can be taken. The principles of preventive medicine are first involved in the preplacement examination and continued during the periodic and special examinations.

Periodic Physical Examination

What should the routine physical examination include? Once again the extent of the examination depends upon the time available, the number of personnel, and the amount of available equipment in the medical department. However, a good periodic examination should include the following: a good history, thorough physical examination, including

*Read in the Section of Occupational Health at the Annual Meeting of the British Medical Association, Birmingham, 1958.

some procedures which often are overlooked, such as an ocular tension determination, an examination of the fundi, palpation of the peripheral blood vessels, rectal examination, and a detailed vision examination; laboratory studies, including urinalysis, haemoglobin estimation, sedimentation rate, blood sugar if over 40 years of age; *x*-ray picture of the lungs; and an electrocardiographic tracing if over 40 years of age. Other laboratory procedures, such as serum cholesterol and non-protein nitrogen estimations and a glucose-tolerance test, should be requested if and when deemed necessary. Unless definitely indicated it is not believed that routine diagnostic *x*-ray procedures such as gastro-intestinal series, barium enemas, or cholecystographies should be done. Likewise, routine serological tests have now been discarded by many.

It is generally conceded that the routine periodic examination is of very definite value. Roberts (1958), in a review of the literature, found that 37.1% of 16,715 individuals examined had significant disease. He also reported that in a tabulation of the results of "routine" laboratory examinations 2.5% of 425,005 cases were abnormal for sugar, 3.2% of 45,961 cases were abnormal for albumin, and 11.91% of 15,619 subjects examined electrocardiographically had abnormal tracings. Franco (1950) found that 149 of 307 executives examined had major medical defects. Cardiovascular conditions accounted for 36% of the defects, and obesity was diagnosed in 25%. Thompson and Staack (1956) found that, in a study of 600 executives, diseases of the arteries and heart made up the largest percentage of newly discovered diseases. These consisted mainly of hypertension and arteriosclerotic heart disease, which occurred in approximately 25% of the cases examined. Hartman (1952), in the proctoscopic examination of executives over 45 years of age at the Mayo Clinic, found that 13% had rectal polyps without symptoms, some of which had undergone adenocarcinomatous changes. In a series of 2,000 cases regardless of age or symptoms he reported that the incidence of rectal polyps was 8%.

During the three and a half months from January 1 to April 15, 1958, a statistical analysis was conducted of 120 periodic examinations in the management group in our company. These cases were taken consecutively. Of the 120 examination, 60 were in the top pilot group aged 35 or older, and 60 were in the management group aged 35 or older. The average age of the pilot group was 40.3 years and of the management group 41.4 years. In the pilot group 38 physical defects were found, eight of which were considered of sufficient significance to warrant follow-up corrective action. In 28 of the 60 pilots examined no abnormalities were found. In the management group there were 78 physical defects, 33 of which were classified as significant, no abnormalities having been found in seven cases. In other words, significant defects were found in approximately 50% of the management group as compared with approximately 13% in the pilot group. There are several reasons for the difference in findings in the two groups—namely, those in the pilot group are specially selected from a physical and health standpoint, a health maintenance programme for this group has existed for many years, and, lastly, as a group they are a great deal more "health conscious" than those not engaged in pilot activities.

Examination Findings

Year in and year out the significant conditions most often disclosed, about which we can take positive and definitive measures, are certain metabolic diseases, including obesity, cardiovascular conditions, and gastro-intestinal conditions including peptic ulcers and parasitic infestations.

Obesity is a common finding, and at times it is difficult to convince the individual that weight reduction is indicated. This is particularly true if no other abnormal findings are disclosed. To reduce, the executive must be properly motivated, be convinced of the potential ill effects of overweight and have the will-power to remain on a low-calorie diet. In those cases where obesity is associated with diabetes or beginning hypertension little or no difficulty is encountered.

Other diseases that have been disclosed are thyroid conditions which are very obvious, and the employees in whom such a condition has been found have been very grateful for the information after corrective action has been taken. Diabetes mellitus is also a relatively common finding. In the original examination of the pilot and executive groups a postprandial urinalysis and blood sugar test is made. It is believed that this procedure is superior to the fasting urinalysis and blood sugar test in recognizing the early or latent diabetic. Applicants are not accepted as pilots if they have diabetes or if they show diabetic tendencies. Postprandial blood sugar tests are made on the pilot group after the age of 35 and on the management group after the age of 40. Prevention of diabetes in the older age group is closely related to the prevention of obesity, control of overweight being particularly important if there is a familial history of diabetes. The close observation of the occasional individual who has a slight glycosuria is also important, since it is believed that transient or alimentary glycosuria is often the precursor of diabetes. It is also a well-recognized fact that the well-controlled diabetic is less apt to develop the early degenerative changes that occur in the uncontrolled diabetic.

In cardiovascular diseases the potential hypertensive individual is seen fairly often, usually associated with obesity. Occasional cases of angina are also disclosed. Electrocardiograms are taken of the pilot and executive applicants so as to have a baseline electrocardiogram for future reference. In the routine physical examination, electrocardiograms are taken annually in the pilot group at 35 years of age and in the executive group at 40. Very infrequently cases of recent coronary thrombosis have been disclosed by the use of the electrocardiogram. Other abnormalities have been found, such as bundle-branch blocks, A–V blocks, etc. Although serious coronary disease may exist with a normal electrocardiogram, depression of RST and T waves in leads I and II and the chest leads may be suggestive of this condition.

In the routine periodic examination it is very rare that hidden asymptomatic malignancy is disclosed. However, those cases in which malignant or pre-cancerous growths can be seen may be picked up and corrective action taken. These include those with lesions involving the skin, nasopharynx, and oral cavity. Although sigmoidoscopy after the age of 45 would be desirable, because of certain limitations we have not been able to include this in our routine examinations.

Certain gastro-intestinal diseases, such as peptic ulcer, have been suspected in a number of cases from the history, and referral has led to corrective action with relief of symptoms. Closely associated with this is the occasional case of cholecystitis and cholelithiasis. Parasitic disease has been a relatively frequent finding consequent upon operation in the tropics.

Mental Stress and Strain

No paper on executive health is complete without some mention of the mental stress and strain which the average executive undergoes in carrying on his duties. In this connexion there is an excellent pamphlet by C. G. Roberts (1951) which states: "The ever-increasing intricacy of industrial techniques accompanied by an equally rapid advance in the complexity of social, governmental, commercial and industrial organizations seems now to be taxing the highest levels of man's mental ability to the full." He writes in considerable detail about the nature of mental skill and the responsibility as related to the executive, the cause of stress with its resultant breakdown in some executives, and the solution.

An important phase of the periodic examination is the conference or discussion with the examinee with a view to obtaining any history of previous or intercurrent diseases and informing him of any defects found during the examination. Of particular importance is a discussion relative to

any stress or strain which he is undergoing, informing him of the importance of the annual vacation, of leaving his work and worries in the office, of hobbies and outside interests, and, finally, of relaxation.

Conclusion

The employee is one of the most valuable assets in any company, and of the employees the management group or executives are particularly valuable because of their training, motivation, and high degree of technical and administrative skill. A health maintenance scheme for the executive is an essential part of any industrial medical programme. Its main object is the detection of disease in its incipiency in order that corrective action may be taken so as to maintain him in good health and increase his longevity and efficiency.

REFERENCES

Franco, S. C. (1950). *Industr. Med. Surg.*, **19**, 213.
Hartman, H. R. (1952). "The Executive and Health." Panel discussion at the Sixteenth Annual Meeting of the Industrial Hygiene Foundation, Pittsburg. Abstracted in *Industr. Med. Surg.*, 1952, **21**, 140.
Irvin, E. A. (1952). "The Executive and Health." Panel discussion at Sixteenth Annual Meeting of the Industrial Hygiene Foundation, Pittsburg. Abstracted in *Industr. Med. Surg.*, 1952, **21**, 141.
Proudfit, A. T. (1957). "Health is Good Business." Industry and Tropical Health, III. Proceedings of the Third Conference—Industrial Council for Tropical Health—Harvard School of Public Health, pp. 5-9.
Roberts, C. G. (1951). "The Health of Executives: Mental Stress and Breakdown." I.W.S. Inc., London.
Roberts, N. J. (1958). *Industr. Med. Surg.*, **27**, 153.
Ruffin, W. H. (1957). "Industry's Responsibility for the Health and Safety of Its Employees." Address at the Annual Meeting of the Industrial Health Council, Birmingham, Alabama, March 12, 1957.
Thompson, C. E., and Staack, H. F. (1956). *Industr. Med. Surg.*, **25**, 175.
Trickett, J. M. (1952). Ibid., **21**, 5.

EFFECT OF PREDNISOLONE ON ANAEMIA ASSOCIATED WITH MACROGLOBULINAEMIA

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In spite of numerous case reports, the pathogenesis of macroglobulinaemia remains obscure. The diversity of clinical features in patients with this abnormality (Waldenström, 1952; Wilde and Hitzelberger, 1954; Long *et al.*, 1955; Ferriman and Anderson, 1956; Mackay *et al.*, 1956, 1957; Jim and Steinkamp, 1956; Martin and Close, 1957; Wanner and Siebenmann, 1957; Kappeler *et al.*, 1957) suggests that it does not itself constitute a disease entity, though it appears in many cases to be associated with neoplastic disease of reticulo-endothelial tissue. In most cases therapeutic measures have not affected the macroglobulinaemia and have failed to shed light on the nature of the anomaly. In view of this, we record the findings in an elderly woman with unexplained anaemia and macroglobulinaemia who has shown marked improvement, in respect both of her anaemia and of her macroglobulinaemia, while being treated with prednisolone.

Case Report

The patient, now aged 73, has attended the Royal Perth Hospital periodically for the past 15 years. Hospital records show that in 1943 and again in 1945 the haemoglobin value of her blood varied between 8 and 9 g./100 ml. No further haematological investigations had been undertaken at those times.

In 1955 she was investigated for anaemia. The clinical history was not informative. She did not suffer from a bleeding tendency. Apart from pallor, clinical examination revealed no abnormality. The liver and spleen were not palpable and the lymph nodes were not enlarged. Anaemia

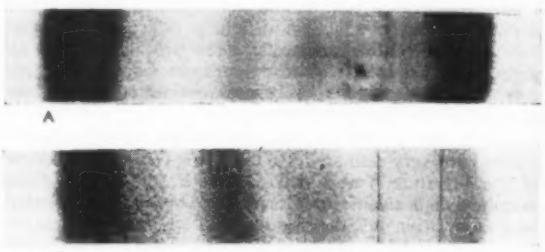

FIG. 1.—Paper electrophoresis of serum. A, Before prednisolone therapy (October, 1956). B, On cessation of prednisolone (June, 1957). The strips have been aligned with the albumin bands to the left.

was of normochromic normocytic type with a haemoglobin value varying between 7.1 and 8.6 g./100 ml. The erythrocyte sedimentation rate was elevated, lying in the range 74 to 155 mm. fall in one hour (Westergren). The total serum proteins as determined by the alkaline biuret reagent of Weichselbaum (1946) were 9.2 g./100 ml. Salt fractionation with 26.9% sodium sulphate solution gave values of 2 g./100 ml. for albumin and 7.2 g./100 ml. for globulin. Paper electrophoresis of serum (Flynn and de Mayo, 1951), using azocarmine B as a protein stain, showed a discrete band of abnormal protein in the γ-globulin region similar to that shown at A in Fig. 1. Bence Jones proteinuria was not present. Examination of sternal marrow and radiological examination of the skeleton failed to reveal any further abnormality, so that a provisional diagnosis of myelomatosis was not sustained. After unsuccessful therapy with a variety of haematinics the patient was treated with blood transfusions.

In 1956 an enlarged lymph node was noted in the left axilla. Further investigations showed that the abnormal serum protein was macroglobulin. It did not migrate from the point of insertion when electrophoresis was carried out in starch gel (Silberman, 1957). On examination in the ultracentrifuge* the serum was found to contain an abnormal component constituting 23% of the total protein (total protein 7.3 g./100 ml.), with a sedimentation constant of 15.3 S. There was also a small amount of a faster sedimenting protein (Fig. 2, A). In addition the serum gave a positive result with the Sia test, although this is not exclusive to macroglobulinaemia.

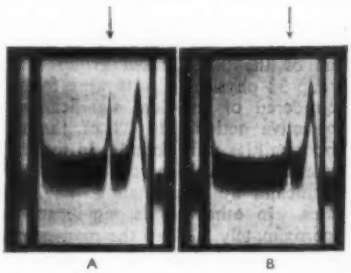

FIG. 2.—Ultracentrifuge pattern of serum. A, Before prednisolone therapy (October, 1956). B, On cessation of prednisolone (June, 1957). Arrows indicate the major macroglobulin component.

At this time the haemoglobin value of the blood was 9.1 g./100 ml. and the haematocrit 29%. The reticulocyte

*Spinco model-E ultracentrifuge; rotor An-A; centrifugal force, number × gravity = 182,000; serum dilution of 1+4 in 0.2 M NaCl solution; *p*H = 7.0; temperature of rotor, 20° C.

count was 2.4% and the Coombs reaction on the patient's red cells negative. Survival of the patient's ^{51}Cr-labelled red cells in her own circulation was normal. The total leucocyte count was 6,600/c.mm., with 53% polymorphs, 37% lymphocytes, 8% monocytes, and 2% eosinophils. The sternal bone marrow was of normal cellularity and showed a moderate increase in lymphocytes, which numbered 29% of all nucleated cells present. There were 2% plasma cells and 16% normoblasts. Further skeletal *x*-ray films showed no abnormality.

Progress is illustrated in Fig. 3. The patient was transfused in October and December, 1956. Prednisolone therapy was then begun at an initial dosage of 40 mg. a day, which was soon reduced to 20 mg. After an initial fall in the haemoglobin value there was a steady improvement, first noticed one month after starting prednisolone. By April, 1957, the haemoglobin value was 14.2 g./100 ml. and the haematocrit 43%. The patient was in good health except for recurrent furunculosis.

In June she developed an acute sinusitis, which progressed to an orbital cellulitis requiring surgical drainage. During her stay in hospital prednisolone therapy was discontinued. The haemoglobin value of the blood fell to 10 g./100 ml. over a period of a week. With the control of infection it

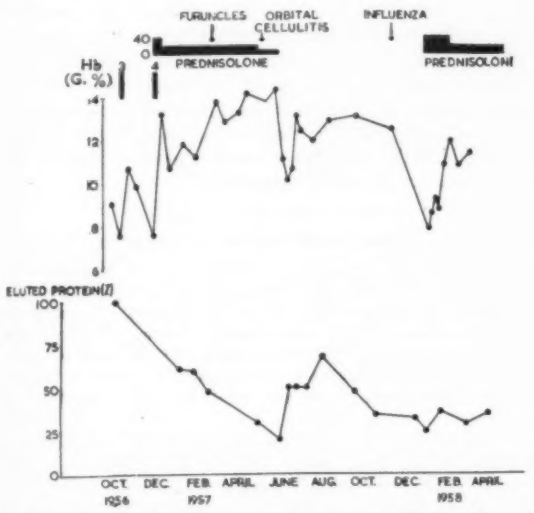

FIG. 3.—Effect of therapy on blood haemoglobin value and concentration of protein migrating electrophoretically as γ-globulin. The figures 3 and 4 refer to pints of blood transfused. Concentrations of dye eluted from the γ-globulin region are expressed as a percentage of the concentration found in October, 1956.

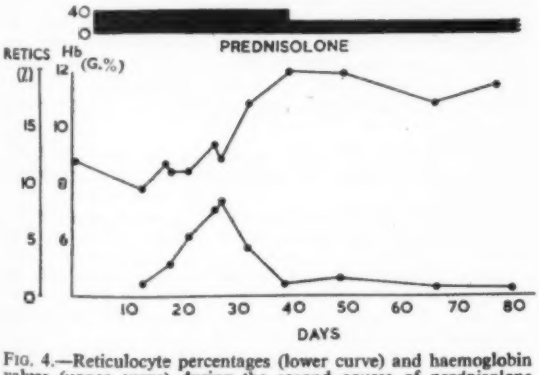

FIG. 4.—Reticulocyte percentages (lower curve) and haemoglobin values (upper curve) during the second course of prednisolone therapy (January, 1958).

spontaneously rose to 12 g./100 ml. and maintained itself at about this level for six months without further therapy.

In December she suffered from influenza. When she was seen one month later, her haemoglobin value was 8.6 g./100 ml. and therapy with prednisolone was recommenced. Subsequent haematological findings are shown in Fig. 4. After 23 days the reticulocytes rose to 8.3%. The haemoglobin value improved shortly after this, and has been maintained since between 12 and 13 g./100 ml. At the time of writing the patient was being treated with a maintenance dose of 10 mg. of prednisolone daily.

Since the beginning of treatment in December, 1956, total serum proteins have been estimated and serum paper electrophoresis performed at frequent intervals. By May, 1957, the dense band of abnormal protein in the γ-globulin position on the electrophoretic strip was distinctly less, and by June, 1957—that is, six months after beginning prednisolone therapy—it had disappeared (Fig. 1, B). Paper electrophoresis at this time showed a slight increase in the α_1- and α_2-globulins. Macroglobulins could still be detected on ultracentrifuge analysis, however, but in less amount than previously (12% of total protein; total protein, 6.4 g./100 ml.) (Fig. 2, B). The Sia test was still positive.

Fluctuations in the amounts of serum protein migrating as γ-globulin were followed by eluting the dye from the relevant area of the electrophoretic strips with 2.5 M sodium hydroxide and measuring the amount of dye photometrically. The results, expressed as a percentage of the initial value, are shown in Fig. 3. Between October, 1956, and June, 1957, there was a steady decrease in protein concentration in the γ-globulin position to 21% of the initial value.

On cessation of prednisolone therapy, concurrent with the onset of orbital cellulitis, the γ-globulin fraction rose sharply, then fell again and has since maintained a fairly steady value. The abnormal band reappeared in the γ-globulin position on the electrophoretic strip one month after prednisolone therapy was stopped and has persisted since then. The second course of treatment had produced no obvious change in the electrophoretic pattern at the time of writing.

Discussion

The mechanism of the anaemia is obscure and its duration uncertain. In the absence of other demonstrable causes of anaemia, it seems reasonable to suggest that the low haemoglobin values recorded in 1943 had the same aetiology as the present anaemia. Although the bone marrow contained an excess of lymphocytes, it is unlikely that the anaemia was due to marrow infiltration, as erythropoiesis appeared adequate. The anaemia was not haemolytic in nature. The degree of marrow erythropoiesis was normal, reticulocyte counts have not been increased apart from therapy, and the patient's red cells gave a negative Coombs reaction. Furthermore, the patient's red cells survived normally in her own circulation. On the other hand, an autoimmune mechanism is suggested by the response to prednisolone therapy. The delayed reticulocyte response noted during the second course of prednisolone therapy suggests that the drug corrected the anaemia through some intermediary mechanism, as specific haemopoietic factors usually show demonstrable effects in a shorter time than this.

A patient of Wilde and Hitzelberger (1954) suffered from autoimmune haemolytic anaemia associated with macroglobulinaemia. As might be expected, this responded to cortisone therapy. Other reports in the literature of cortisone therapy in patients with macroglobulinaemia refer to cases in which the clinical findings resembled lymphosarcoma (Di Guglielmo and Antoninix, 1955; Mackay, 1956; Jim and Steinkamp, 1956). In these patients the therapy had little effect.

The duration of macroglobulinaemia in our patients is uncertain. Almost certainly macroglobulins were responsible for the abnormal serum protein results first noted in 1955.

No cause for macroglobulinaemia has been demonstrated. Although the patient has a marrow lymphocytosis and one enlarged axillary lymph node, the liver and spleen are not enlarged, and the findings differ from many of the cases of macroglobulinaemia so far described—for example, Mackay *et al.* (1956), who suffered from a disease resembling lymphosarcoma. However, it is possible that she may eventually develop this syndrome. It is purely speculative to suggest that lymphocytes might be the source of the abnormal protein.

The alteration in the serum electrophoretic pattern after prolonged prednisolone therapy is of great interest. It should be stressed that the values for γ-globulin shown in Fig. 3 represent both "normal" γ-globulin and macroglobulin. Therefore there are difficulties in interpreting fluctuations in their values, as a diminution in either would result in a decrease of total γ-globulin. However, the decrease in values between October, 1956, and June, 1957, was so marked that it is reasonable to conclude that it represents diminution in macroglobulin concentration. This is also confirmed by ultracentrifuge data, which estimated the macroglobulin to have diminished during this time. Furthermore, the discrete component on the paper electrophoretic strip which was presumably due to macroglobulin (Fig. 1, A) could not be seen on the later strip (Fig. 1, B).

The patient probably shows an increased susceptibility to infection, having suffered from recurrent furunculosis, orbital cellulitis, and a respiratory infection over a period of 18 months. It is possible that she suffers from hypogammaglobulinaemia, demonstration of which would be made difficult by the appearance of macroglobulin in the γ-globulin region on serum paper electrophoresis. Evidence to suggest hypogammaglobulinaemia is furnished by the electrophoretic strip performed in June, 1957 (Fig. 1, B). This shows an intensity of staining in the γ-globulin region within normal limits. As the serum still contained a considerable amount of macroglobulin demonstrable by ultracentrifuge analysis, the normal γ-globulin component was probably reduced.

Summary

The clinical findings are described in the case of an elderly woman who suffered from an unusual form of anaemia and macroglobulinaemia for at least three years. Treatment with prednisolone corrected the anaemia, and this was associated with a diminution in the amount of abnormal protein in the blood.

Dr. John O'Dea, Commonwealth Serum Laboratories, Victoria, carried out the ultracentrifuge analyses. One of us (J. A. O.) has received a grant from the National Health and Medical Research Council.

REFERENCES

Di Guglielmo, R., and Antoninix, F. M. (1955). *Sang.*, **26**, 249.
Ferriman, D. G., and Anderson, A. B. (1956). *Brit. med. J.*, **2**, 402.
Flynn, F. V., and de Mayo, P. (1951). *Lancet*, **2**, 235.
Jim, R. T. S., and Steinkamp, R. C. (1956). *J. Lab. clin. Med.*, **47**, 540.
Kappeler, R., Krebs, A., and Riva, G. (1957). *Schweiz. med. Wschr.*, **87**, 1246.
Long, L. A., Riopelle, J. L., Francoeur, M., Pare, A., Poirier, P., Georgescu, M., and Colpron, G. (1955). *Canad. med. Ass. J.*, **73**, 726.
Mackay, I. R. (1956). *Aust. Ann. Med.*, **5**, 244.
—— Eriksen, N., Motulsky, A. G., and Volwiler, W. (1956). *Amer. J. Med.*, **20**, 564.
—— Taft, L. I., and Woods, E. F. (1957). *Brit. med. J.*, **1**, 561.
Martin, N. H., and Close, H. G. (1957). *Lancet*, **2**, 8.
Silberman, H. J. (1957). Ibid., **2**, 26.
Waldenström, J. (1952). In *Advances in Internal Medicine*, edited by W. Dock and I. Snapper, **5**, 398. Year Book Publishers.
Wanner, J., and Siebenmann, R. (1957). *Schweiz. med. Wschr.*, **87**, 1243.
Weichselbaum, T. E. (1946). *Amer. J. clin. Path.*, **16**, *Tech. Bull.*, **7**, 40.
Wilde, H., and Hitzelberger, A. L. (1954). *Blood*, **9**, 875.

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DEATH CERTIFICATION OF CHILDREN

BY

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The certification of the cause of death is, to the lay person and the administrator, a simple statement of fact. To the pathologist, on the other hand, the "cause of death" is the summation of a number of factors each of which in isolation may be of little importance. At best one knows in part what a person dies with, but not necessarily what he dies from.

The practice of clinical medicine necessitates a concentration on the treatable aspects of disease and a simplification of pathology requisite for a practical approach to the patient. The present form of death certification is designed by necessity for use by clinicians. It has a twofold approach: first, steps in the progress of a major disease, and, secondly, associated disease. Its form is probably as good as can be devised.

The present small survey of 150 deaths was made to assess the efficiency of death certification as carried out in a children's teaching hospital. The resulting figures are statistically significant and show a degree of inaccuracy not generally appreciated.

Material and Method of Survey

Permission is requested to carry out a post-mortem examination on every child dying in the Sheffield Children's Hospital, and is granted in over 90% of cases. At the same time the house officers are asked to indicate on the death certificate that additional information may be available later as a result of the necropsy. The cause of death is revised by the pathologist when the final necropsy diagnosis is made.

Other than this being a consecutive series, no particular selection of the 150 cases was made. The children's ages at death varied from several hours to 12½ years: 78 (52%) died at or before 3 months; 12 (8%) between 4 and 6 months; 24 (16%) between 7 months and 1 year; 23 (16%) between 2 and 3 years; and 13 (8%) between 4 and 12½ years. Thus 137 (92%) of the deaths occurred at or before 3 years of age. The cause of death entered on the death certificate was compared with the final pathological diagnosis made after consideration of the clinical findings, naked-eye pathology, and histology of the case. A record was also made of the duration the child had been in hospital, or, in cases where there had been more than one admission for the same condition, the duration under medical supervision was estimated. Each case was then placed in one of five groups, according to the following criteria.

Group 1.—Cause of death recorded on the death certificate accurate and complete as compared with the pathological findings.

Group 2.—Cause of death accurate in major respects but incomplete in minor points, which did not alter the final diagnosis.

Group 3.—Cause of death inaccurate as compared with the major pathological findings, but minor points accurate.

Group 4.—Pathological findings necessitated a complete revision of the cause of death.

Group 5.—Cause of death as recorded not substantiated by post-mortem examination and no adequate pathological cause of death found.

The following are examples of cases placed in the above groups.

Certified Cause of Death	*Pathological Findings*
Group 1: Girl aged 10 months	
(*a*) Acute adrenal insufficiency. (*b*) Meningococcal meningitis. (*c*) Meningococcal septicaemia.	Congestion of the adrenal glands and histochemically greatly reduced lipoid content. Meningococcal meningitis and septicaemia.
Group 2: Boy aged 4 months	
Tuberculous meningitis.	Tuberculous meningitis. Miliary tuberculosis involving lungs, spleen, liver, kidneys, and meninges. Primary tuberculous complex in right lower lobe of lung and caseating hilar glands.
Group 3: Girl aged 11 days	
(*a*) Bronchopneumonia. (*b*) Congenital meningomyelocele.	Purulent meningitis associated with hydrocephalus due to congenital obstruction between lateral and third ventricles and lumbar meningomyelocele. Oedema of lung (no pneumonia).
Group 4: Girl aged 1 day	
(*a*) Asphyxia neonatorum. (*b*) Breech delivery.	Cerebral haemorrhage due to tears in the falx cerebri and tentorium. Bilateral atelectasis and left-sided pneumothorax. Bilateral adrenal infarction and renal vein thrombosis. Breech delivery.
Group 5: Boy aged 3 weeks	
(*a*) Gastro-enteritis. (*b*) Prematurity.	Post-mortem findings showed wasted mature child, but no adequate cause of death.

Group 1 comprises 23 (15%) cases; group 2, 59 (40%); group 3, 33 (22%); group 4, 28 (18%); and group 5, 7 (5%). If one omits group 5 and combines groups 1 and 2, as those cases where there was no significant change in the certification, and combines groups 3 and 4, where the pathological findings differed considerably from the clinical assessment, the distribution becomes: groups 1 and 2, 82 (55%); groups 3 and 4, 61 (40%). These figures may be regarded as having a statistical trustworthiness—that is, as indications of a firm underlying rate—of about ±15 (±10%) in both cases.

In seven of the 150 cases no pathological diagnosis was eventually made. These deaths all occurred at or before 3 months and represented almost 10% of deaths occurring under 3 months or 5% of all deaths.

Effect of Age.—The ratio of groups 1 and 2 to groups 3 and 4 at different ages is shown in the Table. The figures

Group:	1	2	3	4	5	Total
No. in group	23 (15%) 59 (40%) 82 (55%)		33 (22%) 28 (18%) 61 (40%)		7 (5%)	150
Age at death:						
0–3 days ..	7		13		3	23
4 days–3 months	32		19		4	55
4 months–1 year ..	22		14		—	36
1 year–3 years ..	12		11		—	23
4–10 years	9		4		—	13
Duration under medical care:						
24 hours or less ..	26		17		4	47
2–5 days ..	9		18		1	28
6 days–6 months	36		21		2	59
7 months+	11		5		—	16

give no statistically significant—that is, by tests using the 5% level of significance—or even strongly suggestive evidence that the age of death played any part in determining the accuracy of the cause of death given.

Duration under Medical Supervision.—In assessing the consistency of diagnosis related to the duration of the children's medical care, of 47 children who died after medical care for 24 hours or less, 26 (55%) had an accurate diagnosis. Among the 28 dying after medical care of two to five days' duration, 9 (32%) diagnoses were accurate. Of 59 under care for six days to six months, 36 (61%) diagnoses appeared accurate, and among the 16 cases with medical care of over six months, 11 (69%) were apparently accurate. These figures show no significant difference, and suggest that the duration under treatment is not a major factor in the accuracy of diagnosis.

Discussion

In this series of 150 certifications the correct cause of death, as assessed by the pathologist, was not given in more than 55% of the cases. The accuracy or inaccuracy of the primary entry was influenced very little by the age of the child at the time of death or by the length of time the child was under medical care.

The cause of death entered on the certificate is not necessarily the complete clinical diagnosis made in hospital. That 40% of the total number of cases fell into group 2 (accurate but incomplete) and 40% into groups 3 and 4 suggests that the information submitted on the death certificate was not adequate.

It would seem possible that doctors may have been to some extent influenced by the knowledge that they were initialling the reverse side of the death certificate, but this would affect only the accuracy of certifications as between our groups 1 and 2, but not between groups 2 and 3. The same applies to the use of different terms to describe similar conditions.

The accuracy of the cause of death statistics according to death certification appears to have been of more concern to American workers than to workers in this country (Lane and Holla, 1954; West, 1955), and varying degrees of accuracy of certification have been given as a result of several surveys. We have been unable to find any published figures of this kind for this country.

The Registrar-General is well aware of the problems of accuracy of death certification, and has discussed these in his reports for 1940 and 1950, stressing improvement in certification which follows necropsy.

The extent of the problem is shown in his report for the year 1953 (Registrar General, 1956), where he analyses the certification of causes of 114,642 deaths for the June quarter of 1953, grouping the certifications according to whether the certificate was filled in by the coroner or by the general practitioner, and whether death occurred inside or outside hospital. Great variation in the causes of death in these different groups was found, ranging from 1% disagreement for senility to 70% for pneumonia in the newborn and 75% for meningococcal infections. These certifications obviously involve different groups of cases, and the Registrar-General, by the very nature of the information available to him, is able to compare only the causes of death certified by different groups of people on different cases, but he is not directly able to compare the differing diagnoses in the same cases, the essential for a fair comparison.

Swartout and Webster (1940) report an accuracy of 79% in a study of 8,000 deaths in Los Angeles. They compared the necropsy diagnosis with what they considered would have been the clinical diagnosis, but without reference to the original death certificates. Evans (1949) found an accuracy of only 43% in a study of 3,900 death certificates, basing the findings on his own judgment and without the aid of necropsy findings. Korns and Lintz (1949) found disagreement between the clinical cause of death statement

and pathological findings in 11–20% of 500 hospital cases; and James, Patton, and Heslin (1955) found 71% of original certificates agreeing with necropsy reports in a survey of 1,889 necropsies, but with wide variation within the groups of different diseases, ranging from 21% agreement in the group of arteriosclerotic heart disease to 93% agreement in the group covering tuberculosis. Pohlen and Emerson (1942, 1943) found consistency in diagnosis in 96% of tumours of the heart, compared with 26% in liver tumours, 99% in measles, and 52% in heart disease.

In the above articles, all of which come from public health departments, there is a tendency to state that errors in registration occur between the few larger groups of causes of death, and that the errors in one direction tend to cancel the others out, making the overall statistics relatively accurate. This seems to be an unfortunate argument, as it would appear to give the published figures false accuracy—the type of accuracy obtained by drawing random diagnoses out of a hat—and minimize the danger of arguing from any of the registrar's statistics.

In assessing the accuracy of certification, any comparison made must be between the cause of death as originally certified and the cause of death after survey of all information obtained by clinical and necropsy examination. Inaccuracies in certification arise in two ways: first, a failure to record accurately the knowledge available at the time of death—that is, negligent certification; and, secondly, the inadequacy of the knowledge available at the time of certification.

In a teaching hospital, where every child, particularly an ill child, is under constant discussion, it is unlikely that faulty certification is due to the absence of available knowledge of diseases; on the other hand, certificates are often filled in by junior housemen who have not acquired the art of avoiding terminology that may lead to inquiries by the coroner. The tendency in both of these instances would be towards a more accurate registration if not conventional. We would thus expect the registration in the present survey to be at least as accurate as is likely to occur in the general field of child deaths.

Summary

A survey of the accuracy of the causes of death given to the registrar at a children's hospital showed that almost one-half of the certifications were not correct as judged by the final pathological diagnosis.

We are grateful to Dr. G. H. Jowett, head of the Department of Statistics of the University of Sheffield, for his advice and comments, and to our clinical colleagues for permitting these diagnostic ablutions.

REFERENCES

Evans, A. G. (1949). Referred to by James *et al.* (1955).
James, G., Patton, R. E., and Heslin, A. S. (1955). *Publ. Hlth Rep. (Wash.)*, **70**, 39.
Korns, R. F., and Lintz, W. B. (1949). Referred to by James *et al.* (1955).
Lane, E. A., and Holla, W. A. (1954). *N.Y. St. J. Med.*, **54**, 1523
Pohlen, K., and Emerson, H. (1942). *Amer. J. publ. Hlth*, **32**, 251.
—— —— (1943). Ibid., **33**, 505.
Registrar General (1956). *Statistical Review of England and Wales for the Year 1953*, p. 220. H.M.S.O., London.
Swartout, H. O., and Webster, R. G. (1940). *Amer. J. publ. Hlth*, **30**, 811.
West, H. (1955). Ibid., **45**, 211.

In an address on "The Art and Science of Research," before a sectional meeting of the Manchester Medical Society last month, Dr. J. H. SCOTT, lecturer in anatomy at Queen's University, Belfast, defined research as the intellectual fashion of our time. He compared "useless" and "useful" research as illustrated by the discovery of Nasmyth's membrane in 1839 and of penicillin in 1929, and the part played by chance in certain cases. Discussing Humphry's work on jaw growth in pigs, he pointed out how the results of research were not always applied successfully to the solution of the problems they were supposed to solve. Research, he said, did not primarily depend on money, or on complicated apparatus, but on a peculiar attitude of mind in which curiosity, persistence, and clarity were essential features.

INFLUENCE OF MATERNAL MALARIA ON NEWBORN INFANTS

BY

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It is well known that schizonts of *Plasmodium falciparum* tend to concentrate in the maternal tissue of placentae in the latter half of pregnancy in women infected with that parasite (Blacklock and Gordon, 1925; Garnham, 1938; Bruce-Chwatt, 1952). There has, however, been considerable controversy about what effect this concentration has on the infant born of such placentae to women who are natives of territories where malaria is so prevalent that adult immunity to it is substantial. On the one hand is the Sierra Leone series of Blacklock and Gordon containing "proof of a very complete association between maternal infection of the placenta and death of the child *in utero* or within a seven-day observation period after birth." On the other hand is Garnham's (1949) diametrically opposite assertion from observations in Kenya that "malarial infection in the mother seldom resulted in stillbirths or in death of the infant in the first week," and that "Luo children are unlikely to suffer ill effects from infection in the mother."

Observations in Lagos (Bruce-Chwatt, 1952) have shown that, although there is no apparent correlation there between neonatal mortality and malarial infection of the placenta, yet there are grounds for believing that such infection is a cause of prematurity and, more generally, of the birth of underweight babies. A further report from Southern Nigeria (Archibald, 1956) confirmed these ill effects.

The present paper presents evidence from Northern Nigeria that this infection commonly prevents African infants born there to malarious mothers from reaching their proper weight at birth.

Present Investigation

The evidence was collected from a number of centres in Northern Nigeria where the birth weight of infants was noted, a number of particulars were obtained from the mother, and blood smears were collected from the maternal surface of the placenta and from the mother's finger at the delivery. The blood smears were examined by the regional malaria unit. The group investigated was mainly drawn from deliveries which took place in medical institutions, and was obviously a selected sample of the population. This was underlined by the finding of malaria parasites in only 15% of the smears examined, a rate much lower than the adult parasite rate generally found in the Northern Region of Nigeria.

The present series consisted of 484 women, 73 of whom were infected at delivery with *P. falciparum* (a few were also infected with *P. malariae*). In most of the mothers, parasites could be detected in the smear both from the finger and from the placenta, but in eight cases they were found only in the placenta and in seven only in the finger. Of the 484 pregnancies, 18 were multiple, two of triplets; and of the 504 infants born, 30 (5.9%) were stillborn, 4 (0.8%) were born alive before term, and 470 born alive after pregnancies which had gone to full term. Of these full-term babies, 440 were single deliveries, and it is with these that the further analysis deals.

Table I shows the distribution of birth weights of these babies. Of the 62 infants born from malarious placentae, 13 (20.6%) were premature—that is, weighing 5½ lb. (2,495 g.) or under (W.H.O., 1950)—as contrasted with 31 (8.2%)

TABLE I.—*Record of Birth Weight of* 440 *Infants Born Alive in Single Deliveries After Full-term Pregnancies*

Weight lb.	Weight g.	Infants Born from Malarious Placentae	Infants Born from Non-malarious Placentae
Over 2½–	1,130–	—	1
,, 3–	1,360–	2	—
,, 3½	1,585–	—	2
,, 4–	1,815–	1	4
,, 4½	2,040	5	8
,, 5–	2,270–	5	16
,, 5½–	2,495–	12	50
,, 6–	2,720–	16	65
,, 6½–	2,950–	10	74
,, 7–	3,175–	7	78
,, 7½–	3,400–	3	38
,, 8–	3,630–	1	25
,, 8½–	3,855–	—	11
,, 9–	4,080–	—	4
,, 9½–	4,310–	—	1
,, 10–	4,535–	—	1
Total ..		62	378
Mean weight in group..		6 lb. 2 oz. (2,778 g.)	6 lb. 12½ oz. (3,076 g.)
Standard deviation ..		14·4 oz. (408 g.)	16·4 oz. (465 g.)

TABLE II.—*Record of Birth Weights of* 440 *Infants Born Alive in Single Deliveries After Full-term Pregnancies, Recorded by Race*

Race	No.	Average Weight of Those From Malarious Placentae lb. oz.	g.	No.	Average Weight of Those From Non-Malarious Placentae lb. oz.	g.
Ibo	17	6 5	2,865	124	6 13	3,090
Yoruba ..	26	6 1	2,750	117	6 11	3,035
Hausa ..	11	5 12	2,610	70	6 12	3,060
Fulani ..	—			12	6 11	3,035
Kanuri ..	—			6	6 13	3,090
Others ..	8	6 4	2,835	49	6 13	3,090
	62			378		

of 378 infants born from uninfected placentae. This contrast is significant ($\chi^2=9.7$; $P<0.01$). The mean weight of the 62 infants born from malarious placentae was 10½ oz. (298 g.) less than that of the 378 infants born from uninfected placentae.

The distribution of the 440 single full-term deliveries according to the race to which the mother belonged is shown in Table II. The mean weight of infants born from malarious placentae is consistently lower than that of infants born from uninfected placentae, irrespective of the mother's race. It is of interest to note that the mean birth weight of the infants born from uninfected placentae is very much the same for all racial groups represented in this series, whereas the Hausa infants born of infected placentae were on the average of lower weight at birth than either the Yoruba or Ibo babies. This is consistent with the hypothesis that the immunity developed by the indigenous people of Northern Nigeria, where there is a strictly circumscribed wet season and an explosive seasonal intensification of malaria transmission, is less well established than is that developed by Southern Nigerians who have been bred in conditions where malaria is stable.

An attempt was made to classify the families into which those 440 infants were born in accordance with the standard classes used by the Registrar-General of the U.K. (class I, professional ; class III, skilled workers ; class V, unskilled). This was not very successful because of the large number of families claiming to be "traders," a group which might embrace the merchant prince or the matchbox seller. In fact, the average weight of infants at birth was surprisingly similar for all social classes, although for each class the babies born from malarious placentae were under weight as compared with those born from uninfected placentae. The finding that the birth weight did not improve with social class is not in accord with experience in developed countries, but the explanation may be that in the conservative polygamous society of Northern Nigeria a wife may not enjoy her husband's social advantages. Table III shows the social classification of the 440 infants. The small numbers in this series from social classes I and II indicate that advantage of Western obstetric facilities is not taken by the conservative orthodox leaders of Northern Nigerian society.

TABLE III.—*Record of Birth Weights of* 440 *Infants Born Alive in Deliveries After Full-term Pregnancies Recorded by Social Grouping*

Social Group	Delivered from Malarious Placentae No. in Group	Average Weight at Birth lb. oz.	g.	Delivered from Non-malarious Placentae No. in Group	Average Weight at Birth lb. oz.	g.
I	2	5 10	2,550	1	5 12	2,610
II	1	6 7½	2,935	24	6 12	3,060
III	30	6 1	2,750	206	6 12½	3,075
IV	14	6 5	2,865	76	6 13	3,090
V	4	6 6	2,890	33	6 12	3,060
Not known..	11	6 0	2,720	38	6 11½	3,050
	62	6 2	2,780	378	6 12½	3,075

The influence of maternal parity on the weight of an infant at birth is well known. In the present small series it was found that, in each class, the infants from malarious placentae were less heavy than the others, but the overriding importance of parity was shown by the poor weights of babies born to primiparae.

Discussion

The present series of cases differs from those previously published from Southern Nigeria (Bruce-Chwatt, 1952 ; Archibald, 1956) in that the effect of malaria on birth weight is more pronounced in this northern than in previous southern groups. This is shown in Table IV.

The proportion of mothers in the series who at the same time showed infection in both blood and placenta was also much higher than has usually been found. In these women in Northern Nigeria, 79% of infections were manifest in both blood and placental smears. Schwetz and Peel (1934) reported a similar coincidence (74%) from the Congo, but in Blacklock and Gordon's (1925) Freetown series only 20% of infections were found in blood and placenta at the same time ; in Garnham's (1938) Kenya series it was 59%, and in Bruce-Chwatt's (1952) Lagos group 43%. It is probable that these differences can be explained as being due to variations in the immunity of the mothers. Probably coincident infection of blood and placenta indicates that the woman has not succeeded in mastering the infection. On that postulate, the high coincidence of infection of both blood and placenta in the present series would signify that these women did not have a strong immunity. This is consistent with earlier impressions that immunity to malaria in Northern Nigeria is not firmly established.

TABLE IV.—*Influence of Malarial Infection of Placenta on Birth Weight of Nigerian Babies*

Series	Premature In Malarious	Premature In Non-malarious	Average Weight In Malarious	Average Weight In Non-malarious
Northern Nigeria	13/62 (20·6%)	31/378 (8·2%)	6 lb. 2 oz. ± 14·4 oz. (2,778 ± 408 g.)	6 lb. 12½ oz. ± 16·4 oz. (3,708 ± 465 g.)
Southern Nigeria	20/68 (29·4%)	65/395 (16·5%)	6 lb. ± 10 oz. (2,722 ± 283 g.)	6 lb. 6 oz. ± 14·6 oz. (2,892 ± 414 g.)
Lagos	15/73 (20·5%)	26/237 (11·0%)	5 lb. 13½ oz. ± 17·4 oz. (2,651 ± 493 g.)	6 lb. 2 oz. ± 15·1 oz. (2,778 ± 428 g.)

Summary

A series of 440 full-term deliveries of single infants is analysed to elicit the effect produced by *P. falciparum* infection of the placentae on the weight at birth of African babies.

The series is analysed by race, social class, and maternal parity, and in each group the effect of malaria infection has been that infants born from infected placentae have a mean weight at birth below that of those born from uninfected placentae.

The effect of *P. falciparum* infection is more pronounced in the present series than in previous groups collected in Southern Nigeria.

The series showed an unusually high proportion of mothers with both blood and placental infections detectable at the same time.

It is postulated from the last two observations that the mothers in the present series were not succeeding in mastering their parasitaemia, and this is thought to strengthen earlier impressions that malarial immunity is not firmly established in the population of Northern Nigeria.

I am indebted to those members of the Medical Department of the Northern Region who assisted in the investigation, and to Dr. R. A. B. Dikko, Acting Principal Medical Officer of the Endemic Diseases Division of the Ministry of Health of the Region, for permission to publish this paper.

REFERENCES

Archibald, H. M. (1956). *Bull. Wld Hlth Org.*, **15**, 842.
Blacklock, D. B., and Gordon, R. M. (1925). *Ann. trop. Med. Parasit.*, **19**, 327.
Bruce-Chwatt, L. J. (1952). Ibid., **46**, 173.
Garnham, P. C. C. (1938). *Trans. roy. Soc. trop. Med. Hyg.*, **32**, 13.
—— (1949). *Ann. trop. Med. Parasit.*, **43**, 47.
Schwetz, J., and Peel, Mlle (1934). *Trans. roy. Soc. trop. Med. Hyg.*, **28**, 167.
World Health Organization (1950). Wld. Hlth. Org. techn. Rep. Ser., No. 27.

ISOLATION OF E.C.H.O. VIRUS TYPE 9 DURING AN OUTBREAK OF MENINGO-ENCEPHALITIS

BY

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During July, 1956, an epidemic of lymphocytic meningo-encephalitis with marked myalgia occurred in Newton-le-Willows, Lancashire (Lyle, 1956). At the same time type I poliomyelitis was occurring in Manchester and Coxsackie B meningitis in Stockport. Neither the epidemiology nor the symptomatology of the Newton-le-Willows outbreak suggested non-paralytic poliomyelitis or the clinically indistinguishable Coxsackie meningitis, but attempts were made in tissue cultures to isolate an agent from the faeces of seven patients.

Virus Studies

Faecal suspensions were prepared in saline and purified by high-speed centrifugation to remove contaminating bacteria. The resulting supernates were inoculated into stationary monolayer tube cultures of monkey-kidney cells prepared by a modification of Youngner's (1954) method.

Two specimens were tested shortly after receipt and both were found to be highly toxic to the culture cells, non-specific degeneration occurring within 24 hours of inoculation.

The residue of these, together with five other prepared specimens, were stored in a low-temperature refrigerator (−25° C.), as prolonged storage has been found to diminish the toxicity of faecal extracts.

At the end of four months all the specimens were tested in monkey-kidney cultures as before, and also in stationary HeLa-cell cultures. Negative results were obtained in both types of culture with specimens from two adults and one child taken on the third, seventh, and sixteenth days of illness respectively. Of the other four specimens from children, two showed slight degenerative change in kidney cells with no effect in the HeLa strain, while the other two showed no change in either type of culture. In all four cases subinoculation of culture fluid was made to fresh kidney- and HeLa-cell cultures. It was not until the fourth blind passage that definite cytopathogenic degeneration was noted in HeLa cells, although it was evident in all the monkey-kidney cultures at the second passage. A further series of blind passages in tissue culture was made with the three negative specimens previously referred to, without results at the fifth passage, when the material was abandoned. Lesions were not produced in 1-day-old mice either by original faecal suspensions or by tissue-culture fluids from cultures showing cytopathogenic effect inoculated by the intracerebral or subcutaneous routes.

Neutralization tests on tissue-culture fluids were carried out with antisera against poliovirus types 1, 2, and 3, and Coxsackie virus types B1–B5, with negative results. Tests with E.C.H.O. virus type 9 antiserum gave positive results identifying the agent.

Significant rises in neutralizing antibody in E.C.H.O. 9 virus were demonstrated by Dr. D. A. J. Tyrrell, of the Virus Research Laboratory, Sheffield, and by Dr. A. D. Macrae, of the Virus Reference Laboratory, Colindale, in 8 out of 10 cases from which paired sera were available, including one with negative faeces, and three of the four cases from which isolations were achieved. The fourth case had a high neutralizing antibody titre in the first serum specimen, and this was unchanged 15 days later.

Clinical Notes.—The ages of the children from whom isolations of virus were made were 5, 6, 7, and 12 years. All had fever, headache, and enlargement of posterior cervical lymph nodes. In three of the cases axillary glands were also involved, and two of these had inguinal gland enlargement as well. Central nervous symptoms were not prominent, but one child had a positive Kernig sign with slight neck rigidity, one had a transient loss of knee-jerks, and a third had some neck stiffness.

Discussion

The association of E.C.H.O. virus type 9 with cases of aseptic meningitis has been reported from West Virginia (Committee on E.C.H.O. viruses, 1955), and Belgium (Nihoul *et al.*, 1957). In the United Kingdom, Tyrrell and Snell (1956) and Tyrrell (1957, personal communication) recovered this agent from cases similar to Lyle's occurring in the Sheffield area in September, 1956, and a closely related agent with the additional property of pathogenicity for suckling mice has been isolated during outbreaks in East Suffolk (Boissard *et al.*, 1957), Leicester (Rotem, 1957), and Sweden (Wesslén *et al.*, 1958).

The initial negative findings in HeLa-cell cultures suggest that these are less sensitive than monkey-kidney cells for the primary isolation of this virus, and this is confirmed by the findings of Jamieson *et al.* (1958), who isolated five strains in monkey-kidney cells, but could not detect any virus using HeLa-cell cultures.

Although repeated passage in HeLa cells may lead to adaptation to this cell strain (Archetti *et al.*, 1957), this is not normally a practicable diagnostic procedure.

Summary

An agent serologically identical with E.C.H.O. virus type 9 has been isolated from four cases of lymphocytic meningo-encephalitis with myalgia and a rash occurring in an epidemic outbreak.

The expenses of this work were defrayed by a grant from the National Fund for Poliomyelitis Research. Clinical details of cases were made available by Dr. W. H. Lyle, to whom I express my thanks.

REFERENCES

Archetti, I., Weston, J., and Wenner, H. A. (1957). *Proc. Soc. exp. Biol. (N.Y.)*, **95**, 265.
Boissard, G. P. B., Stokes, L. J., Macrae, A. D., and MacCullum, F. O. (1957). *Lancet*, **1**, 500.
Committee on E.C.H.O. viruses (1955). *Science*, **122**, 1187.
Jamieson, W. M., Kerr, M., and Sommerville, R. (1958). *Lancet*, **1**, 581.
Lyle, W. H. (1956). Ibid., **2**, 1042.
Nihoul, E., Quersin-Thiry, L., and Weynants, A. (1957). *Amer. J. Hyg.*, **66**, 102.
Rotem, C. E. (1957). *Lancet*, **1**, 502.
Tyrrell, D. A. J., and Snell, B. (1956). Ibid., **2**, 1028.
Wesslén, T., Eriksson, S., Ehinger, A., and Zetterberg, B. (1958). *Arch. ges. Virusforsch.*, **8**, 183.
Youngner, J. S. (1954). *Proc. soc. exp. Biol. (N.Y.)*, **85**, 202.

Medical Memoranda

Pituitary Deformity from Carotid Compression—a Potential Hazard in Pituitary Ablation

One of the ways in which certain hormone-dependent tumours are treated is by ablation of the pituitary body. Among the methods used is one involving the injection of a radioactive substance into the gland. This is performed by needle puncture of the floor of the sella turcica via the nasal route. The procedure is done under some form of *x*-ray control, but is nevertheless one that requires great skill if numerous important anatomical relations of the pituitary are to escape injury. The object of this paper is to draw attention to a change in the carotid arteries which makes them more vulnerable and puncture or irradiation of them an added hazard of this form of treatment.

The normal relations of the carotid arteries to the pituitary are such that they do not impinge on the lateral extremities of the organ.

I have frequently observed, *post mortem*, that atheromatous internal carotid arteries may be varicose to a greater or less degree. Where the carotid dilatation is slight one sees small oval depressions on the sides of the pituitary. With further ectasia of the vessels the pituitary becomes hollowed inferolaterally, and in extreme varicosity the pituitary is bilaterally compressed about its middle and acquires a dumb-bell shape. The accompanying photograph shows the appearance in such an advanced case and also, what is often seen, that the carotids are unequally affected, so that the dumb-bell is asymmetrical. It measures 4.5 mm. across its waist instead of the normal 12 to 13 mm.

Upper aspect of dumb-bell type of pituitary deformity. Posterior lobe is below.

The youngest subject in whom I have seen the most severe degree of the deformity was a man of 57. Clearly the encroachment towards the midline of the carotid arteries is a potential hazard in closed operations in the fossa. The condition is mentioned by Henke and Lubarsch (1926), and a photograph in their handbook shows the appearance of the sella turcica in such a case. It was not noted by Beattie and Heasman (1958) in a recent study of 82 pituitaries from elderly mental patients with and without hypertension. (Sheehan and Summers (1949) do not mention it under "Extrasellar tumours—miscellaneous," but remark about this group in general: "In many cases there is an astonishing lack of symptoms despite quite gross compression of the pituitary.") In the cases I have seen there were no post-mortem findings or clinical data to suggest that hypopituitarism existed, nor would it be expected with such a volume of surviving glandular tissue.

I thank Dr. N. F. C. Gowing and Mr. W. P. Greening for their advice and help.

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REFERENCES

Beattie, M. K., and Heasman, M. A. (1958). *J. Path. Bact.*, **75**, 83.
Henke, F., and Lubarsch, O. (1926). *Handbuch der Speziellen Pathologischen Anatomie und Histologie*, vol. 7. Springer, Berlin.
Sheehan, H. L., and Summers, V. K. (1949). *Quart. J. Med.*, **18**, 319.

Tuberculous Meningitis as a Cause of Mental Deficiency

Some 17 years ago I saw a series of cases of tuberculous meningitis admitted to a psychiatric observation ward on account of acute psychotic features (Kirman, 1943). At that time there was no effective treatment for the disease, and residual effects were not a problem. Tuberculous meningitis was always looked upon as a fatal disease until the introduction of streptomycin. It was not, therefore, a cause of mental deficiency.

A SERIES OF CASES

The first case admitted to the Fountain Hospital was in 1951, since when a total of 13 cases have been admitted (Table I). The condition is best described as a meningoencephalitis, and unless response to treatment is prompt permanent damage to mental capacity is inevitable. Our hospital accommodates 600 children with mental deficiency, and the admission rate is approximately 80 a year, being the majority of mentally defective children admitted from the counties of London and Surrey. The cases admitted represent the intermediate group between those who die and those whose illness results in lesser degrees of brain damage expressed as educational retardation or behaviour disturbance. It is difficult to draw conclusions from small numbers, but our experience does suggest that there has been an improvement in the situation since 1949–50 and that this disease should very seldom in the future be a cause of mental defect.

Social factors are very important in our group of cases. In part this is the result of tuberculosis in the family (Table II), which may reduce the income or the ability to provide a home, but low incomes and inadequate housing appear often to have anteceded the infection.

The mental grade in these cases was: idiot in 7, imbecile in 4, and educationally subnormal in 2. After much patient effort it was possible to return to the educational system the two children who proved to be above imbecile level. The main handicap in these two cases was restlessness, and they later became stabilized.

TABLE I.—*Tuberculous Meningitis*

Year:	1948	1949	1950	1951	1952	1953	1954	1955	1956	Total
Onset ..	1	4	2	3	1	0	1	1	0	13
Admission	—	—	—	1	6	2	0	0	4	13

The ages in years at onset were <1 in 5 cases; 1– in 5; 2– in 1; 3– in 1; 4– in 0; and 5– in 1.

TABLE II.—*Tuberculosis in Family*

Father died ..	.. 2	Sibling died	.. 1	Other relatives	.. 3
Father ill ..	.. 4	Sibling ill	.. 3	Lodger ..	.. 1
Mother ill ..	.. 3				

Physical disabilities found were: blindness in 6, strabismus in 5, hemiplegia in 3, spastic diplegia in 2, hydrocephalus in 2, deafness in 2, and epilepsy in 2.

In our experience tuberculous meningitis has about the same importance at the present time as kernicterus as a cause of mental defect. It is about six times as important as cretinism or congenital syphilis, and accounts for about one-third of the number of cases produced by phenylketonuria.

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REFERENCE

Kirman, B. H. (1943). *Brit. J. Tuberc.*, **37**, 63.

The Ministry of Agriculture, Fisheries, and Food has reminded farmers of the very serious danger to anyone entering a grain bin or silo when the grain is being run out of the bottom of the bin. A vortex is created and anyone on the grain is liable to be drawn down and suffocated. Two fatal accidents have recently occurred in this way.

Reviews

HORMONE PRODUCTION IN ENDOCRINE TUMOURS

Ciba Foundation Colloquia on Endocrinology. Volume 12. *Hormone Production in Endocrine Tumours.* Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Maeve O'Connor, B.A. (Pp. 351+xii; illustrated. 48s.) London: J. and A. Churchill, Ltd. 1958.

Laboratory studies of the endocrinological background of human breast cancer need the support of the experimental approach if we are materially to increase our understanding of the general biological significance of hormone dependence or, and to a far greater extent, of the state of independence which is so often its tragic sequel. This report of a Ciba Colloquium reveals the encouraging possibility that the study of hormone dependence in naturally occurring or experimentally produced animal tumours may lead us farther towards the solution of this urgent problem. It records twelve major contributions and eight short papers given by workers from Denmark, Sweden, the Netherlands, the United States of America, and Great Britain. Half the papers dealt with hormone-dependent animal tumours, the majority being hormone-induced. These included pituitary tumours in mice (Furth) and in hamsters (Horning), in the thyroid (Leathem), the ovary (Mühlbock and also Gardner), the adrenal cortex (Woolley), and the testis (Huseby). In most of these papers accounts of the author's own work were prefaced by short, valuable general surveys of each problem. The other papers reported intensive investigations into tumours of the human endocrine organs and included reports on the iodinated compounds in the serum in thyroid cancer (Tata), and the study of body fluids in patients having functioning tumours of the gonads and adrenal cortex. In this paper given by Ralph Dorfman, the chairman of the symposium, the results, obtained by all the refinements of modern techniques, were correlated with biosynthetic studies of the tumour itself in a successful attempt to clarify the biosynthesis of the steroid hormones. Other papers dealt with the histology, enzymology, and hormone production in tumours of the human adrenal cortex (Symington and Currie), the estimation of urinary steroids in the differential diagnosis of hyperplasia and neoplasia of the adrenal cortex (Robinson), the bioassay of urinary gonadotrophins in hydatidiform mole and uterine chorion epithelioma, and of gonadotrophins, androgens, and oestrogens in malignant testicular tumours (Hamburger).

As in all Ciba Colloquia, the discussions reached a high critical standard by the inclusion of workers of long experience in their own subject. The omission of these discussions would certainly rob these Colloquia of what is probably their most valuable feature. For the more general reader, two commendably clear accounts of hormone dependence in animal tumours by W. U. Gardner, of the Yale University School of Medicine, are outstanding. This is the twelfth of the "Colloquia on Endocrinology" and includes a carefully compiled cumulative index of Volumes 1 to 12.

GEOFFREY HADFIELD.

TRENDS IN ANAESTHESIA

Modern Trends in Anaesthesia. Edited by Frankis T. Evans, M.B., B.S., F.F.A.R.C.S., D.A., and T. Cecil Gray, M.D., F.F.A.R.C.S. (Pp. 318+ix+13; illustrated. 67s. 6d.) London: Butterworth and Co. (Publishers), Ltd. 1958.

In any branch of medicine in which rapid development is going on there is a real need for a bridge between the textbook, which rarely includes matters at the spearhead and in which the fundamentals may be out of date by the time the book appears, and the specialist journals, which may be nearly impossible for one individual to cover adequately. The "Trends" series bridges this gap admirably. This newest number on anaesthesia lives up to the reputation of the others. In the space of only 300 pages most of the important aspects, both theoretical and practical, of anaesthesia are dealt with by well-chosen experts who do their job well. For example, W. D. M. Paton discusses very competently the nature of the mechanisms involved in neuromuscular transmission and block. Current work on the behaviour of the motor endplate to relaxants, and on the role played by the small myelinated gamma motor fibres in reflex action, is particularly clearly summarized. C. Gray gives a picture of the present status of hypothermia that could not be bettered for brevity and completeness. Both the methods of cooling patients and the physiological effects that follow are described in the light of modern work. While the indications are clearly expounded, the risks and limitations of the methods are no less so.

Other equally outstanding contributions come from A. B. Dobkin on pulmonary ventilation and control during anaesthesia, J. J. Bonica on the place of regional anaesthesia, and I. C. Geddes on local analgesics. There are 17 other chapters, however, all full of interest and well documented with references. The authors have been gathered widely. Besides Britain, the United States (J. J. Bonica, E. M. Papper), Canada (A. B. Dobkin), and Sweden (E. Nilsson) are represented. Illustrations, mostly graphs, are comparatively few (30) and far between. There is little hesitation in describing this book as an important and valuable contribution to anaesthetic literature. At its present standard a life of many editions is assured.

W. W. MUSHIN.

GENERAL SURGICAL OPERATIONS

Orr's Operations of General Surgery. By George A. Higgins, M.D., F.A.C.S., and Thomas G. Orr, Jr., M.D., F.A.C.S. Third edition. (Pp. 1,016+vi; illustrated. £7.) Philadelphia and London: W. B. Saunders Company. 1958.

This well-produced and lavishly illustrated volume of over 1,000 pages is intended for general surgeons. This raises the question, What (or who) is a general surgeon? By looking through this book one may find some limitations which the authors would impose. We find, for example, that partial gastrectomy is well described but total gastrectomy is omitted; that there is a description of partial pancreatectomy but removal of the whole pancreas is not included. The only operations on the skull which are described are for fracture, extradural and intradural bleeding, and, curiously enough, arterial encephalography. All operations on the brain are excluded, and there appears to be no mention of operations on the mastoid process in the book. But there is still a wide range left. There are detailed descriptions of removal of a lung or larynx, excision of coarctation of the aorta or an abdominal aneurysm, and all types of amputation (including the hindquarter); even vaginal hysterectomy and vesico-vaginal fistula are included. It is, of course, impossible to set a limit for any particular general surgeon. Experience, opportunity, personal skill and inclination, all have a part in determining which operations a surgeon will be prepared to perform. It would be a retrograde step to make too hard-and-fast limitations. Certainly most general surgeons will find this book useful.

ZACHARY COPE.

CHILDHOOD ASTHMA IN KANSAS

The Management of Childhood Asthma. By Frederic Speer, M.D. (Pp. 116+xii; illustrated. 36s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

This small volume is essentially concerned with the management of extrinsic allergic factors in asthmatic children as they are found in Kansas in the United States. It is emphasized that foods and inhalants are the basic causes of asthma in children, and only by careful investigation and treatment on these lines can success be obtained. Foods are considered the "leading" allergens, milk, chocolate-cola, egg, and "legumes" accounting for just over 80% of food allergens. The limitations of skin testing for foods are discussed, and the emphasis is on detection of food allergens by thorough trial dieting. In the chapter on the

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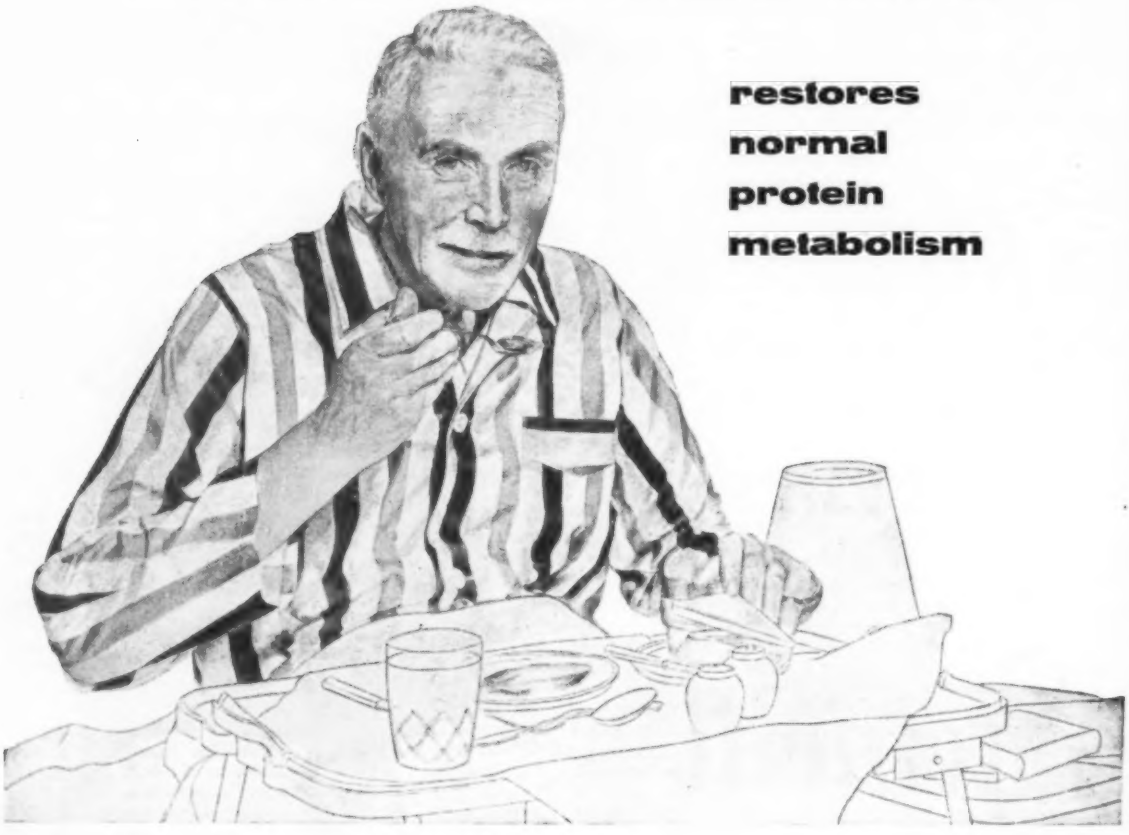

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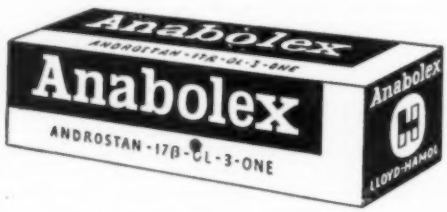

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management of problem cases the author writes: "The problem of intractable asthma which is at once the most important and difficult is that of hidden or latent food allergies. It is a *difficult* problem because hidden food allergens may become manifest only when the child is under stress"—a viewpoint which has little support in Great Britain.

The investigation and treatment of inhalant allergens follows conventional lines, but it is surprising to us in Britain to find that *Alternaria* mould spores are considered of outstanding importance, occurring in 67% of all inhalant allergens, ragweed-pollen sensitivity occurring in 43%, house dust in 38%, *Helminthosporium* in 23%, and grass pollen in 18%. The mould-spore and pollen counts found in Kansas are set out. These findings, both botanical and clinical, emphasize the considerable differences which exist between Kansas and Great Britain. In the latter country there is no ragweed, *Helminthosporium* is rarely caught on our slides and culture plates, and *Alternaria* occurs only in relatively small numbers. "Psychic stress" is a recognized contributory factor in certain cases, and infection is considered as a common and treacherous problem in asthmatic attacks, especially in infants; but comparatively little space is given to these aspects of asthma. The treatment of the asthmatic is well set out and includes advice on cortisone and corticotrophin dosage. It is an easily read and well-produced book.

D. A. WILLIAMS.

ENCHONDRAL DYSOSTOSES

Wesen und Bedeutung der Enchondralen Dysostosen. By Hans Mau. (Pp. 219+xii; illustrated. DM.27.) Stuttgart: Georg Thieme Verlag. 1958.

In this book on the "Nature and Significance of Enchondral Dysostoses" Dr. Hans Mau has with great application collected and correlated a large number of skeletal abnormalities whose origins lie in the maldevelopment of the epiphysis or the metaphysis. He has reconsidered the aetiology, pathology, and clinical, biological, and radiological aspects of the congenital disturbances of ossification called chondrodystrophy or multiple dyschondroplasia, and with this he has also studied gargoylism and chondrodystrophia calcificans. The object of the work is to relate various deformities one to another under the term "enchondral dysostoses." By this is meant a hereditary metaphysial or epiphysial ossification—collectively uncomplicated and without resemblance to tumour formation and varying in severity. To this group also belong asymmetrical forms and some cystic forms, even if these are not hereditary.

A very wide range of bony abnormalities is included in this definition; to quote a few: cleido-cranial dysostosis, osteogenesis imperfecta, Ollier's disease, osteochondritis vertebralis, dyschondroplasia, varieties of coxa vara, and osteochondritis dissecans. It is not Dr. Mau's fault that many of these syndromes, recognized entities and single cases, have in many instances several names of a complicated nature, in English and in other languages. Some of these names appear even more terrifying and incomprehensible in German. This makes hard reading. Dr. Mau, however, makes his main points, and deserves great credit for drawing attention to the essential similarity of many skeletal abnormalities and their hereditary basis, and for emphasizing the need to examine the whole skeleton if the general manifestations which frequently accompany a particular deformity are not to be overlooked—for example, dwarfism and skeletal disproportion or coxa vara. Of the propriety of casting his net so widely only time will tell. In discussing osteochondritis dissecans the massive, often bilateral, form with a hereditary basis is not clearly distinguished from the minute, more common, post-traumatic form, but so many conditions are included that the discussion of each one must inevitably be short.

The book will stimulate those who read it to take a deeper interest in hereditary and epiphysial defects, and to examine their cases more carefully both clinically and radiologically to exclude defects elsewhere. Of the primary cause of these defects the author can say nothing new. A rationalized approach such as he gives should lead to wider observation and the collection of associated defects which may eventually assist in solving the mystery of their formation.

J. G. BONNIN.

INTERNATIONAL CARDIOLOGY

L'Année Cardiologique Internationale: Tome VI. By Camille Lian. (Pp. 360; illustrated. 2,000 fr.) Paris: Expansion Scientifique Française. 1957.

The "International Cardiological Year" is edited, as before, by Dr. Camille Lian. There are 26 contributors, all working on the Continent of Europe. The first paper, dealing with obliterative arterial disease, recommends "raubasine" (rauwolfia) and the subcutaneous injection of radioactive waters. A discussion of the regimens for treating heart failure warns against too rigid restrictions, which may be worse than the malady. There is an interesting discussion of the effects of mitral disease on the lungs, and of the relief by valvotomy. The treatment of acute pulmonary oedema is helped by anti-foam preparation, such as silicones if an irritating substance has been inhaled; otherwise aerosol in alcohol is recommended. The clinical picture of the premonitory period of myocardial infarction is discussed. Transient subendocardial or subpericardial lesions are shown in the electrocardiogram. Anticoagulants and vasodilators may prevent actual infarction. In the prevention of myocardial infarction by anticoagulants it is suggested that this be used only in grave cases; the difficulties of proper control and really efficacious treatment are emphasized. For Stokes–Adams attacks isopropylnoradrenaline is favoured. In the diagnosis of myocardial infarction a rise of transaminase in the serum is found in all cases in the first three days; it does not occur in pulmonary infarction. Hydatid cysts of the heart are the subject of a paper. There is an interesting article on the familial incidence of derangements in the metabolism of cholesterol. Ammi visnaga (khellin) is thought to be of some use in effort angina.

This is a useful collection of papers from various countries showing the trends of thought and interest on various important topics that stand out at the present time. Many papers have references; in some it is a pity that only names are given, but no references at all.

TERENCE EAST.

The Dr. Albert Wander Memorial Lectures have been delivered in Berne biennially since 1952. The first three lectures have recently been published in one volume (*Dr. Albert Wander Gedenkvorlesung*, Heft 1; 89 pp., illustrated; Hans Huber, Berne and Stuttgart, 12.40 Swiss francs) and comprise "Das Höhenklima und sein Einfluss auf den Menschen," by Alexander von Muralt, "The Conquest of Bacterial Disease," by Sir Howard Florey, and "Sulfamides et Biologie," by Jacques Tréfouël.

In 1947 the Universities Federation for Animal Welfare produced the first edition of its *Handbook on the Care and Management of Laboratory Animals*. The considerable advances in knowledge of the subject since that time have now been incorporated in a second edition, obtainable from the Federation, 7a, Lamb's Conduit Passage, London, W.C.1 (pp. 951, illustrated: 70s.). Joint editors of the new edition are Mr. A. N. Worden and Dr. W. Lane-Petter, and Sir Harold Himsworth has contributed a foreword. The first 16 chapters deal generally with housing, breeding, and other considerations common to laboratory animals, while the remainder of the book discusses some 50 individual species or groups of species. Relevant references are appended to each chapter and there is a full index.

In *New and Non-Official Drugs 1958* the Council on Drugs of the American Medical Association describes drugs that have been newly introduced. Short monographs give chemical and biological details, notes on therapeutic administration and dosage, and contraindications. The drugs are "evaluated on the basis of available scientific data and reports and investigations." Published by J. B. Lippincott and Co., the book is marketed in Great Britain by the Pitman Medical Publishing Co. Ltd. for 30s.

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PHYSICAL ACTIVITY AND CORONARY DISEASE

In Britain coronary thrombosis, angina, and arteriosclerotic myocardial degeneration are now registered as the cause of about one-quarter of all male deaths over the age of 40. Even though the rising incidence of ischaemic heart disease may not be so dramatic as is sometimes stated, it is one of the principal sources of ill-health and premature death in middle age.

Investigations into the causes of coronary heart disease in Britain have been principally directed towards an assessment of the significance of intravascular thrombosis,[1] defects in blood coagulation,[2 3] hormonal factors,[4] and physical activity.[5] J. N. Morris and his colleagues[6] have reported that rapidly fatal ischaemic heart disease is more common in the sedentary drivers of London's double-decker buses than in the more physically active conductors, and more common in the sedentary postal and telephone clerks than in physically active postmen. Moreover, the bus conductors and postmen, when they did suffer from coronary disease, had it less severely than drivers and clerks. On the basis of these observations Morris advanced the hypothesis that men in physically active jobs have a lower incidence of ischaemic heart disease than men in sedentary jobs, and that the disease is not so severe in physically active workers, in whom it tends to present first as angina pectoris. Subsequently, a study of the sizes of the uniforms worn by bus drivers and conductors indicated that the drivers were larger and presumably fatter than the more active conductors when they entered the transport service[7]; thus factors other than physical activity, such as selection of occupation, appear to be operating.

Nevertheless, Dr. J. N. Morris and Dr. Margaret Crawford in a remarkably interesting study printed in the opening pages of this issue have gone far towards confirming their hypothesis. Throughout Britain they have had the co-operation of many pathologists, who each completed a standard form of inquiry for 25 unselected consecutive necropsies on men between the ages of 45 and 70 years. From an analysis of the reports of 5,000 necropsies the incidence of large discrete areas of myocardial fibrosis (greater than 1.5 cm. in any one dimension), multiple small myocardial scars, and coronary atheroma was related to occupational activity during life. There were 1,700 different descriptions of occupations, and these were classified into light, active, and heavy jobs according to the physical activity demanded. In 3,800 necropsies on patients dying from some cause other than coronary disease twice as much ischaemic myocardial fibrosis was found in light workers (13.4%) as in heavy workers (6.8%). This was more obvious in cases with large fibrous myocardial infarcts than in those with smaller multiple scars, and an excess of large fibrous infarcts was particularly evident in the younger age groups. In contrast to this striking correlation between ischaemic myocardial fibrosis and physical inactivity, there was only slightly more coronary occlusion in light workers and no significant difference in the prevalence of severe coronary atheroma between the three groups of occupational activity. The necropsies performed on patients whose deaths were due to clinical coronary heart disease numbered 1,200, and heavy workers were the least common among these.

Morris and Crawford include in this article a study of physical activity in relation to the incidence of ischaemic heart disease by social class. In 1910 Osler[8] commented on the "remarkable fact with which we are all familiar—that angina pectoris is an affection of the better classes, and not often seen except in private practice." After the 1931 census the Registrar-General[9] published the standardized mortality ratio for various diseases according to occupation. Physicians and surgeons headed the list of deaths from coronary disease. The proprietors of wholesale businesses, the legal profession, and the Church followed close behind. In contrast, chemical workers, agricultural workers, stone quarriers, and certain grades of miners had an unusually low death rate from coronary disease. The pattern is much the

[1] Duguid, J. B., *Lancet*, 1949, **2**, 925.
[2] O'Brien, J. R., *Amer. J. med. Sci.*, 1957, **234**, 373.
[3] Poole, J. C. F., *Brit. med. Bull.*, 1958, **14**, 253.
[4] Oliver, M. F., and Boyd, G. S., *Lancet*, 1956, **2**, 1273.
[5] Morris, J. N., and Heady, J. A., *Brit. J. industr. Med.*, 1953, **10**, 245.
[6] —— *et al.*, *Lancet*, 1953, **2**, 1053, 1111.
[7] —— Heady, J. A., and Raffle, P. A. B., ibid., 1956, **2**, 569.
[8] Osler, W., ibid., 1910, **1**, 697.
[9] *Registrar-General's Decennial Supplement, England and Wales 1931*. Part IIa, "Occupational Mortality," 1938, H.M.S.O., London.
[10] Ryle, J. A., and Russell, W. T., *Brit. Heart J.*, 1949, **11**, 370.
[11] Morris, J. N., Heady, J. A., and Barley, R. G., *Brit. med. J.*, 1952, **1**, 503.
[12] Arnott, W. M., ibid., 1954, **2**, 887.
[13] Stocks, P., *Lancet*, 1951, **1**, 351.
[14] Zoll, P. M., Wessler, S., and Schlesinger, M. J., *Circulation*, 1951, **4**, 797.
[15] Eckstein, R. W., *Circulat. Res.*, 1957, **5**, 230.

same to-day. J. A. Ryle and W. T. Russell[10] interpreted these findings as a reflection of the exacting character of sustained mental effort required in intellectual and responsible occupations.

J. N. Morris, J. A. Heady, and R. G. Barley[11] showed that the incidence of first attacks of angina and myocardial infarction is twice as high in general practitioners as in consultants and specialists, whose rates of morbidity and mortality are similar to those of members of other professions than medicine. They wisely refrained from offering any explanation of these findings, but these various social differences in the incidence of coronary disease are often attributed to the different emotional tensions and environmental stress of contrasting occupations. It is very difficult to judge what is stressful to any particular individual, and W. M. Arnott[12] has emphasized that excessive psychological stress has never been shown to be more harmful in the professional and intellectual classes than in the less privileged classes. Indeed, it might be argued that the stress factor could be expected to operate more in communities where poverty, insecurity, and starvation are rife. P. Stocks[13] examined the mortality from coronary disease in the various social classes, relating it to the physical demands of occupation, and suggested that the differences could be as well explained by physical activity as by the mental stress of the occupation. Morris and Crawford have confirmed this suggestion by reporting that the incidence of ischaemic myocardial fibrosis shows a steady fall from the professional and executive classes (13.3%) through the skilled technician groups to the unskilled labourers (7.8%). While supporting the popular belief that ischaemic heart disease is commoner in the better-off sections of the community, they found that this trend disappeared when the social classes were analysed in terms of the physical activity of the occupations in them. Thus the frequent occurrence of ischaemic heart disease in the professional and executive classes seems to be more dependent on physical inactivity than on high standards of living, education, skill, and responsibility.

As the authors are undoubtedly aware, their study is open to several criticisms. The nature of only the last occupation has been recorded, and thus no allowance has been made for any alteration in physical activity consequent upon a change of occupation. It is a common aspiration of manual workers to progress towards executive and more sedentary jobs, particularly if they have an ambitious and conscientious personality. It is also possible that the development of ischaemic myocardial fibrosis could so reduce the exertional capacity of active and heavy workers as to induce them to seek lighter jobs and yet be insufficient, once they had changed their work, to lead to symptoms. Details about earlier employment might therefore have been informative. Again, no account of leisure activity has been given; this is often erratic and hard to assess, but some apparently sedentary workers are probably more active than they seem from analysis of their physical activity at work alone. Much depends on the accuracy of the description of occupation, which is so often casually recorded in case histories. An omission which many will regret is a record of the weight or obesity of the patients in this series. Without further knowledge, therefore, many will not be able to accept unconditionally Morris and Crawford's hypothesis that work entailing physical activity is a protection against ischaemic heart disease.

Although greater physical activity may possibly reduce intravascular clotting, probably its more important effect is to increase the coronary collateral circulation. Physical exertion increases the cardiac output and the coronary blood flow, but not necessarily in parallel. Most adults have some degree of coronary atherosclerosis and rigidity of the coronary arteries; it might be expected, therefore, that coronary flow will not always keep pace with the increase in cardiac output. Minimal myocardial anoxia could develop, and this has been shown to act as a stimulus to the formation of collateral coronary anastomoses.[14] Indeed, effective collateral vessels develop more profusely in dogs with coronary obstruction if the dogs are exercised.[15]

Further studies are required, but if they support the proposition that habitual physical activity might reduce the incidence of ischaemic heart disease, then there are certain practical implications to be considered. Artificial restrictions should not be placed on the physical activity of patients who already have symptoms of coronary disease, and, within reason, the patient should be allowed to decide his own level of exercise tolerance. In this way a better coronary collateral circulation might be encouraged, and, in theory at least, the extent of a further myocardial infarct might be limited. The rest of us in sedentary occupations should endeavour to take more exercise regularly, although sudden and violent exertion is probably undesirable, particularly in middle age. Studies of the protective action of leisure activities are now indicated. Meanwhile some good might be done by walking part or all of the way to work and by being less dependent on cars, buses, and lifts. The active in mind should make time to remain active in body.

LUMBAR PUNCTURE

Examination of samples of cerebrospinal fluid obtained by lumbar puncture is one of the most important and valuable diagnostic measures utilized in the investigation of neurological cases. Consequently it is tempting to carry it out as a routine in all varieties of neurological disease. This is a temptation worth resisting firmly, because lumbar puncture may in certain cases carry serious dangers to life, while at the least it may occasionally prove to be a painful procedure, no matter how skilful the operation; severe and incapacitating headache follows in some cases. Thus the decision to carry it out needs careful consideration of each individual case, with an attempt to weigh the risks against the possible information it may yield.

Of all the contraindications to lumbar puncture, raised intracranial pressure due to a focal intracranial lesion is perhaps the most complete. In such a case removal of spinal fluid from the lumbar theca may result in sudden death from compression of the brain stem due either to herniation of the cerebellar tonsils into the foramen magnum, or of the medial part of one or both temporal lobes through the tentorial hiatus. Hence papilloedema, or clinical suspicion of a cerebral tumour, particularly in the posterior fossa, is usually a contraindication, though it is generally safe to carry out the procedure with caution in patients who are believed to have an infiltrating neoplasm in one or other cerebral hemisphere but who show no clinical evidence of increased intracranial pressure. No hard-and-fast rules are applicable to every case, since in tuberculous meningitis, for instance, there may be papilloedema, but lumbar puncture is nevertheless essential for diagnosis. This fact only serves to underline the necessity for regarding this investigation as a matter for individual decision, based on clinical appraisal and experience. Local cutaneous and spinal abnormalities such as skin sepsis and ankylosing spondylitis are among other possible contraindications. The belief once widely held that lumbar puncture may promote relapse in disseminated sclerosis no longer appears to be valid, and in certain patients presumed to be suffering from this disease the investigation is essential in order to exclude surgically remediable compression of the spinal cord.

Once the decision to carry out a lumbar puncture is made, all possible steps should be taken to make the procedure as tolerable as possible for the patient. Prior sedation may occasionally be necessary, with paraldehyde for noisy or restless patients, or with sodium amytal or methylpentynol for the apprehensive. This is not the place to describe many details of technique, except to suggest that the old-fashioned wide-bore needle with a built-in two-way tap should no longer be used, since much finer needles of the Harris type are more satisfactory. There is general agreement that infiltration of the skin and interspinous ligaments with local analgesic should be carried out, but deep infiltration is unnecessary. With these precautions, and with the patient relaxed on his left side with the back arched and the knees drawn up to the chin, the insertion of the needle should be virtually painless. Care is taken not to insert the needle too far, as it may then enter vertebral veins, causing bloody contamination of the fluid, or alternatively it may enter the annulus fibrosus of an intervertebral disk and possibly be responsible for subsequent disk prolapse.

The avoidance of the unpleasant headache which so often follows the examination, even in normal people, is a matter of some difficulty. The headache is believed to be due to continual seepage of cerebrospinal fluid into the extradural space through the hole in the dura left by the exploring needle. It is certainly true that, the smaller the needle which is used, the less frequent are these headaches. It might be expected that in patients whose cerebrospinal-fluid pressure is lower than the average these headaches would tend to be more frequent, but no such correlation has been detected. Some recent observations of R. J. Brocker[1] are of interest. He points out that if the patient lies supine after a lumbar puncture the spine is flexed, a negative pressure is created in the extradural space, and cerebrospinal fluid is drawn out through the hole in the dura. He suggests that, in order to separate rather than cut the dural fibres with the point of the needle, it should be inserted with the bevel vertical instead of horizontal; then, immediately the needle has been withdrawn, the patient should be turned into the prone position and should remain there for three hours. Brocker suggests that maintenance of this position, which causes some degree of spinal hyperextension, increases the pressure in the extradural space and prevents leakage of cerebrospinal fluid. His own observations certainly seem to support these views, for, in 894 patients who remained prone for three hours following lumbar puncture, headache occurred in only 4 (0.5%), while the incidence of headaches in 200 patients who were kept supine was 36.5%. Some confirmation of these observations from other workers would be welcome, but it seems that assumption of the prone position immediately after lumbar puncture may be an effective means of reducing the incidence and severity of headache.

[1] Brocker, R. J., *J. Amer. med. Ass.*, 1958, **168**, 261.

ADMINISTRATION OF OXYGEN TO INFANTS

Oxygen has for long been an accepted part of the treatment of so many disorders and a life-saving remedy in emergencies that it is sometimes overlooked that there may be certain hazards associated with its administration. Unfortunately these hazards are most often encountered just when the need for oxygen is greatest—namely, in premature infants immediately after birth. At this time it is certainly a potentially iatrogenic agent; the two diseases for which it has been held responsible, at least in part, are retrolental fibroplasia and hyaline membrane disease.

Retrolental fibroplasia first attracted attention after the report by T. L. Terry[1] in the U.S.A. in 1942. Within a short time it became clear that cases of the disease were widespread in many different countries and the incidence of blindness in babies rose alarmingly. It was not until 1953 that oxygen was finally incriminated[2] and, with the recognition of the fact that high concentrations must be avoided, the incidence of retrolental fibroplasia fell as precipitously as it had arisen. Nevertheless in the comparatively few years of its existence it brought blindness to many hundreds of infants. It is now general practice in all maternity units and in children's hospitals admitting premature infants for the concentration of oxygen to be carefully controlled and not allowed to exceed 40%.

The recognition of hyaline membrane disease is also of recent origin. It is almost entirely confined to premature infants, is particularly common after caesarean birth, and is usually fatal. The exact cause is not known, but experimental work suggests that oxygen may play an important part. The latest report, from Sweden, by R. Berfenstam and colleagues,[3] suggests that excessive oxygen may act by diminishing the ciliary activity in the bronchial tree and thereby favour the retention of the material forming the hyaline membrane. In rabbits exposed to oxygen in 70–80% concentration for 48 hours the ciliary action was both quantitatively and qualitatively reduced. Berfenstam and colleagues suggest that premature infants, adapted to low oxygen tension *in utero*, may show evidence of oxygen toxicity at relatively low concentrations in extrauterine life, and they stress the necessity for determining what level of oxygen concentration is safe for such infants in their earliest days after birth. They also found experimentally that excessive oxygen caused vascular damage with increased capillary permeability, and the resulting exudate probably furnished the main part of the hyaline membrane.

In view of these toxic properties of oxygen the methods of administering it to premature infants require careful supervision. Whereas in later infancy the problem may be how to keep the concentration sufficiently high in such emergencies as laryngotracheobronchitis, bronchopneumonia, and cardiac failure, the problem in the emergencies associated with the establishment and maintenance of adequate respiration in premature infants is how to do this with an oxygen concentration not exceeding 40%. There are many ways of enriching the infant's atmosphere with oxygen, some simple, some complex; they include administration through a rubber or plastic face mask periodically; by nasal catheter or by a catheter passed into the stomach; and by oxygen tents and complicated incubators incorporating constant humidity and temperature control, carbon-dioxide absorption, and atomized mists to accompany the oxygen. Whenever a closed method is used, repeated estimations of the oxygen concentration are desirable. Simple "perspex" bell covers are notoriously deceptive in the rate at which the oxygen tension rises, even with a flow of only 1 litre per minute, and not all flowmeters are sufficiently accurate for the physician to assume that if the flow remains below a certain rate the oxygen tension will not rise above a certain level. Dry oxygen is more irritating to the lungs than when it is adequately moistened, but bubbling it through a Woulfe's bottle does not produce sufficient moisture unless there are means for maintaining the humidity of the infant's surroundings at or above 65%.

A simple device for administering oxygen to infants and young children has recently been described by R. Batson and W. C. Young.[4] It consists of a transparent plastic open-top box. Its advantages are that, as oxygen is heavier than air, its maximal concentration is near the bottom of the box, where the infant lies; adequate therapeutic levels can be obtained in 10 minutes; the nursing care of the child is easy and does not interfere with the maintenance of the oxygen supply; there is less likelihood of claustrophobia; and carbon dioxide is adequately disposed of without the necessity for soda-lime. In an emergency they improvised an efficient makeshift with a transparent plastic laundry bag suspended from the cot sides; the infant was placed in the bag and oxygen supplied through a nebulizer with the outflow tube directed into the lower level of the bag. In the treatment of acute bronchopneumonia and similar emergencies in infancy such a simple, cheap, and easily constructed home-made apparatus must have great value. Certainly the open-top box method offers many advantages in the nursing of sick children who require oxygen therapy.

[1] Terry, T. L., *Amer. J. Ophthal.*, 1942, **25**, 203.
[2] Ashton, N., Ward, B., and Serpell, G., *Brit. J. Ophthal.*, 1953, **37**, 513.
[3] Berfenstam, R., Edhund, T., and Zettergen, C., *Acta Paediat.* (*Uppsala*) 1958, **47**, 527.
[4] Batson, R., and Young, W. C., *Pediatrics*, 1958, **22**, 436.

STEROIDS IN IDIOPATHIC STEATORRHOEA

In 1951 T. P. Almy[1] described a patient with refractory idiopathic steatorrhoea who responded well to treatment with A.C.T.H. There was a striking increase of weight, cessation of diarrhoea, return of normal appetite, and disappearance of abdominal distension. At about the same time A. B. Taylor and his colleagues[2] reported favourable results from the use of cortisone in six patients, the improvement being accompanied by increased absorption of fat and diminished faecal loss of nitrogen. D. Adlersberg and his colleagues[3 4] used oral hydrocortisone with beneficial results. They found that the free alcohol of hydrocortisone was superior to hydrocortisone acetate. It also appeared to have some advantages over A.C.T.H. and cortisone in that it was

effective in small doses without side-effects. "No adverse effects, no habit formation, and no resistance to this mode of therapy have been noted."

While these observations were being made in America, European workers were more occupied with the Dutch discovery[5,6] that a gluten-free diet would render children with coeliac disease symptom-free and permit normal growth and development. These original observations were rapidly confirmed[7,8] and it has since been found that a considerable proportion of adult patients with idiopathic steatorrhoea respond well to a gluten-free diet.[9,10] Indeed, the consensus of opinion is that idiopathic steatorrhoea in the adult is the same disease as coeliac disease in children, though tropical sprue appears to be a different illness.

J. M. Finlay and K. J. R. Wightman[11] compared the effects of cortisone and a gluten-free diet in adult cases of idiopathic steatorrhoea and found that cortisone rapidly relieved the diarrhoea and improved the absorption of fat. On the other hand, the response to a gluten-free diet, though more slow, was more complete. In terms of practical medicine, the corticosteroids have generally appeared to have only a small part to play in the treatment of idiopathic steatorrhoea, although useful in initiating a remission especially when given in combination with a gluten-free diet. However, M. J. Lepore[12] has now described six patients whom he has maintained in good health on long-term treatment with corticosteroids in quite small doses, such as 40 mg. or less of hydrocortisone a day, for periods of up to seven years. When corticoids have been stopped, these patients have relapsed, sometimes in two or three weeks and sometimes after a longer period. Lepore remarks that in his experience the best responses to a gluten-free diet have been seen in patients with a definite history of coeliac disease in childhood; none of these six patients treated with adrenal steroids had such a history.

The mode of action of adrenal steroids in idiopathic steatorrhoea remains problematical. However, J. W. Paulley's[13] original observation that the mucosa of the small intestine is histologically abnormal in idiopathic steatorrhoea has been abundantly confirmed by recent studies.[14-17] It is possible that the adrenal steroids act directly on this abnormal mucosa and block whatever mechanism is responsible for defective absorption in this disease. Even though we do not understand the mode of action, Lepore's work suggests that maintenance treatment with small doses of corticosteroids is worthy of trial in patients who fail to respond well to a gluten-free diet. It is probably wise to continue with the gluten-free diet in addition.

[1] Almy, T. P., *Ann. intern. Med.*, 1951, **34**, 1041.
[2] Taylor, A. B., Wollaeger, E. E., Comfort, M. W., and Power, M. H., *Gastroenterology*, 1952, **20**, 203.
[3] Adlersberg, D., Colcher, H., and Wang, C. I., *A.M.A. Arch. intern. Med.*, 1953, **92**, 615.
[4] Colcher, H., Drachman, S. R., and Adlersberg, D., *Ann. intern. Med.*, 1953, **38**, 554.
[5] Dicke, W. K., *Transactions of the 6th International Congress on Paediatrics (Zurich)*, 1950, 117.
[6] Weijers, H. A., and Van de Kamer, J. H., *Fat Absorption in Normal and Abnormal Infants and Children with Special Reference to Coeliac Disease*, 1950, T.N.O. Publ. No. 113. Utrecht Centraal Inst. voedingsonderzock.
[7] Anderson, C. M., Frazer, A. C., French, J. M., Gerrard, J. W., Sammons, H. G., and Smellie, J. M., *Lancet*, 1952, **1**, 836.
[8] Sheldon, W., and Lawson, D., ibid., 1952, **2**, 902.
[9] French, J. M., Hawkins, C. F., and Smith, N., *Quart. J. Med.*, 1957, **26**, 481.
[10] Schwartz, M. K., Sleisenger, M. H., Pert, J. H., Roberts, K. E., Randall, H. T., and Almy, T. P., *Gastroenterology*, 1957, **32**, 232.
[11] Finlay, J. M., and Wightman, K. J. R., *Ann. intern. Med.*, 1956, **45**, 191.
[12] Lepore, M. J., *Amer. J. Med.*, 1958, **25**, 381.
[13] Paulley, J. W., *Brit. med. J.*, 1954, **2**, 1318.
[14] Shiner, M., *Lancet*, 1956, **1**, 85.
[15] Doniach, I., and Shiner, M., *Gastroenterology*, 1957, **33**, 71.
[16] Sakula, J., and Shiner, M., *Lancet*, 1957, **2**, 876.
[17] Hines, H. W., and Adlersberg, D., *Gastroenterology*, 1958, **35**, 142.

DOES B.H.C. DAMAGE THE BONE MARROW?

When a new chemical is introduced into general use under a variety of conditions, a heavy responsibility rests on those called upon to give an opinion on its safety for such uses. At an early stage reliance must be placed on the reaction of experimental animals and that of the people who may handle the compound during its manufacture and early development. By these standards B.H.C. (benzene hexachloride, "gammexane") seemed at least as safe as D.D.T., on whose heels it followed closely. It seemed to be safe for use as an insecticide under a wide variety of conditions, and has been widely used in public health work and agriculture. There is no evidence that it will produce poisoning except (rarely) under conditions of gross carelessness or misuse.[1-3] Enormous quantities have been sprayed in malaria control, and often the wettable powders are dispensed by hand and the suspension stirred by hand. When the same methods were used to handle dieldrin, poisoning soon became evident.[4]

Now, however, a few scattered reports are appearing implying that exposure to B.H.C. can cause agranulocytosis or leukaemia. When such cases are discussed together, as in a recent study of leukaemia in cousins,[5] the record against B.H.C. at first sight appears rather black. Nevertheless caution is advisable before jumping to conclusions. No cases have been reported among the most heavily exposed people. Have they been missed? This is possible. Among 79 people with illness following the misuse of B.H.C.[2] there is no report of agranulocytosis, though these people were anaemic—they were also undernourished. It is worth considering the exposure of the victims of these blood disorders: two cousins unloaded bags of B.H.C. for a month about eight months before their illness[5]; one man sprayed crops for two days just before his illness[6]; another disinfested clothes and other articles at irregular intervals in full protective clothing[7]; another worked in a shop in which a vaporizer had been installed a few months earlier.[8] Both cases of agranulocytosis had a preceding infection. One had received 2.5 g. chloramphenicol; the other had had 6 g. sulphonamide, 0.5 g. chloramphenicol, 200 mg. phenylbutazone, and a suppository containing amidopyrine. It may thus be unreasonable to blame the vaporizer for the

[1] Buck, A. A., and Pfannemüller, L., *Arch. Toxikol.*, 1957, **16**, 328.
[2] Danopoulos, E., Melissinos, K., and Katsas, G., *Arch. Ind. Hlth.*, 1953, **8**, 582.
[3] Heiberg, O. M., and Wright, H. N., ibid., 1955, **11**, 457.
[4] Patel, T. B., and Rao, V. N., 1958, *Brit. med. J.*, **1**, 919.
[5] Jedlicka, V. L., Hermanska, Z., Smida, I., and Kouba, A., *Acta. med. scand.*, 1958, **161**, 447.
[6] Friberg, L., and Martensson, J., *Arch. Ind. Hlth.*, 1953, **8**, 166.
[7] Albahary, C., Dubrisay, J., and Guérin, *Arch. Mal. prof.*, 1957, **18**, 687.
[8] Marchand, M., Dubrulle, P., and Goudemand, M., ibid., 1956, **17**, 257.

illness. If agranulocytosis were caused by B.H.C., surely it would be much more common among people who handle large quantities of the drug with no particular precautions. At any rate it is among such people that any attempt to substantiate that suspicion should be made.

An unfortunate gap in the technique of experimental toxicology is the lack of any method for reproducing in animals those conditions such as agranulocytosis seen with such regularity after certain drugs are widely introduced into medicine. Indeed, little or nothing is understood about the mechanism of the reaction except that it is believed to be a form of hypersensitivity and therefore presumably has some immunological basis. Meanwhile if anyone is tempted to sum the individual reports referred to here and make out a case against B.H.C., it is also worth bearing in mind the caution expressed by each author about his own case. Such qualifications in the appraisal of individual cases tend to get lost when generalizations are made.

THE EPIDERMIS IN ECZEMA

In patients whose inborn pattern of reaction to stress is dermatological and eczematous, the catarrhal reaction which emanates from the papillary capillaries is thought to result from the action of metabolites derived from epidermal cells. J. H. Allison and F. R. Bettley,[1] by some neatly executed experiments, show that the epidermis of the normal skin in such eczematous patients is "fragile" in the sense of being abnormally sensitive to injury. Cantharidin has a toxic effect on epidermis, causing acantholysis, and can be used to produce a blister on the skin. Allison and Bettley show that the acantholytic effect of cantharidin is more marked in the eczematous han in the non-eczematous subject and is not influenced by the oral administration of prednisone. There is also a significantly greater exudation of fluid and it contains a higher proportion of protein in the atopic subject than in the normal or in those suffering from urticaria or from so-called seborrhoeic, hypostatic, or nummular eczema. The urticarial subjects were chosen as controls because they were presumed to have an abnormality of vascular response leading to increased capillary permeability.

These results suggest that over and above any effect, direct or indirect, of cantharidin on capillary walls, in the atopic subject the vulnerable and damaged epidermal cells contribute something which affects the permeability of the vessel walls, influencing the quantity and character of the plasma exudate. The authors do not give clinical details, but it is presumed that under the not very satisfactory term atopic they imply a state of chronic eczema starting at infancy and associated with hay-fever or asthma and often with urticaria. This syndrome, also known as the asthma-eczema-prurigo syndrome or Besnier's prurigo, may be associated with xeroderma and sometimes with a special type of juvenile cataract. It is commonly familial. It would have been interesting to know the results of similar investigation with cantharidin in patients with simple xeroderma, but so far as it goes it does perhaps support the suggestion previously put forward that Besnier's prurigo is in part dependent upon an ectodermal defect.[2]

The investigation is important in suggesting some difference in mechanism between eczema of the inherited or atopic variety and other forms of acquired eczema. The significantly altered reaction in the patients with atopic disease, pointing to a peculiar epidermal component in the reaction, may explain in part the difficulties encountered in treating them and should direct attention to measures which act more directly upon the epidermis.

[1] Allison, J. H., and Bettley, F. R., *Brit. J. Derm.*, 1958, **70**, 331.
[2] Ingram, J. T., ibid., 1955, **67**, 43.

LEUCINE AMINOPEPTIDASE

Enzyme tests are being increasingly used in diagnosis. One of the latest enzymes to be studied is leucine aminopeptidase, a proteolytic enzyme which hydrolyses leucine-containing peptides. It is present in many tissues but is particularly abundant in duodenal juice and in the kidney and liver. It can be estimated by a colorimetric method based on the formation of an azo dye.[1] Normal values for serum average 142 units for men and 130 for women, while urinary activity is about 82 units in men and 43 units in women. A. M. Rutenburg and his colleagues[2] have recently analysed the results from determinations of leucine aminopeptidase in over 300 patients with a variety of clinical conditions. Exceptionally high levels in serum and urine—three or four times normal—were found in patients with carcinoma of the pancreas, whether jaundiced or not. The serum activity was significantly higher than that encountered in cases of gallstone in the common duct, in which the level of aminopeptidase was moderately raised. Acute pancreatitis also results in a moderate, though transient, rise in contrast to acute cholecystitis, in which enzyme activity is normal. Serum aminopeptidase is also increased in patients with parenchymatous liver disease, but again to a less extent than in carcinoma of the pancreas. A striking finding was the increased urinary levels in patients with malignant lymphomata, in spite of normal or only slightly raised activity in the serum. Cancer at sites other than the pancreas did not affect aminopeptidase except when liver metastases were present.

It is difficult at this stage to predict the diagnostic value of this particular enzyme. Normal values rule out carcinoma of the pancreas, and its estimation may be of use both in this disease and in the malignant lymphomata. Further work may possibly show that it is a means of differentiating not only extra-hepatic from parenchymatous jaundice, but also jaundice due to stone from that caused by a carcinoma of the head of the pancreas.

[1] Goldbarg, J. A., and Rutenburg, A. M., *Cancer (Philad.)*, 1958, **11**, 283.
[2] Rutenburg, A. M., Goldbarg, J. A., and Pineda, E. P., *New Engl. J. Med.*, 1958, **259**, 469.

Drug Treatment of Disease

THE CONTROL OF THE SALE OF POISONS AND DANGEROUS DRUGS

BY

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"It is more than likely that the annual global injury and number of deaths due to poisoning (excluding alcohol, hashish, opium, and other addictions) exceeds by far the destruction which would be caused by an annual atomic bomb explosion in a heavily built-up area."[1]

Parliament in Great Britain has recognized the risk to the community from poisoning—homicidal, suicidal, and accidental—and for many years has been concerned with legislative measures to lessen the risk. This has been accomplished by restricting the availability of toxic substances to the public. The legislature has distinguished between substances which are toxic and substances which are not only toxic but also lead to addiction. Substances in the first category are described as poisons and those in the second as dangerous drugs.

The current law dealing with these matters is contained in the Pharmacy and Poisons Acts and the Dangerous Drugs Act, 1951, together with their relevant regulations and orders. Owing to the rapid development of the drug industry and the large number of toxic substances being brought into medical use, frequent alterations in the poisons regulations have been necessary. This has made them rather complicated. The following is an attempt to produce a short and simplified account of the present position.

The principal Act is the Pharmacy and Poisons Act, 1933. Section 17 of this Act instructed the Secretary of State to cause the Poisons Board to prepare and submit to him a list of the substances to be treated as poisons and also to divide the list of poisons into two parts—Part I to contain all the poisons in medical, scientific, dental, and veterinary use, and Part II to contain substances in common use.

Substances in Part I of the Poisons List can be sold only by authorized sellers of poisons—namely, registered pharmacists. Substances in Part II of the Poisons List can, however, be sold by authorized sellers of poisons and by listed sellers of poisons—namely, persons whose names are on the local authority's list. Examples of these are ironmongers and seedsmen who have made successful application to the local authority for inclusion on the list.

Section 23 of the 1933 Act gave the Secretary of State power to make rules for the sale or supply of the listed poisons. This is the authority for the various rules and orders which at present control the manufacture, supply, and sale of poisons.

The most important rules and orders made in accordance with this section are those of 1935. These rules listed poisons to which detailed regulations for supply, purchase, and storage apply. The list appeared in the First Schedule to the regulations, and this is the origin of the term "First Schedule poison." The rules also listed a number of poisons which were to be obtained only on a medical prescription, and these were contained in the Fourth Schedule of the Rules; this is the origin of the term "Fourth Schedule poison." The other schedules to the Act detail further restrictions, exemptions, and regulations which are chiefly of interest to sellers of poisons.

When new substances are made available and recognized as poisons they are added to the Poisons List, and if they are to be subject to special restrictions they are added also to the First Schedule. If it is considered that they should be available only on a medical prescription, then, in addition to being added to the Poisons List and the First Schedule, they are also added to the Fourth Schedule.

Restrictions on Poisons in First Schedule

These restrictions are concerned mainly with the labelling of the poisons, the recognition of the purchaser as a suitable person to obtain the poison, and the recording of the details of the transaction. A knowledge of them is of importance chiefly to those doctors who dispense their own medicines. Doctors who require First Schedule poisons can obtain them from authorized sellers of poisons either by attending at the premises and signing the poisons register recording the sale or by providing a written order.

Doctors cannot supply poisons except as medicines for their patients. The medicine must be labelled with the name and address of the practitioner. If it is a liquid for external application, the container must bear the words "For external use only" and the name of the article—for example, "The Liniment." The container must be impervious to the poison and must be distinguishable by touch. If the poison is supplied in any way, apart from personal administration, a record must be made in a book showing the date of supply, the ingredients of the medicine, the amount of the poison, and the name of the patient. These records must be made on the same day as the medicine is supplied or, if this is not practicable, on the following day.

All the potent medicinal poisons are included in the First Schedule—for example, arsenical poisons, barbiturates, ergot, hydrocyanic acid.

Restrictions on Poisons in Fourth Schedule

The Fourth Schedule contains a list of substances which can be sold by retail only on a prescription given by a registered medical practitioner, registered dentist, or registered veterinary surgeon. In cases of emergency, when the doctor is unable to give the prescription immediately, the authorized seller may provide the poison in accordance with the doctor's instructions, provided the doctor undertakes to forward the appropriate prescription within 24 hours. The prescription for a Fourth Schedule poison must be in writing, must be signed and dated by the person giving it, and, if it is not a National Health Service prescription, must specify his address. The prescription must also specify the name and address of the person for whose treatment it is given, and must also show the total amount of the substance to be supplied with the dose to be taken.

Restrictions are also imposed upon the dispenser of Fourth Schedule poisons. He cannot dispense these poisons more than once unless the prescriber has stated that they may be dispensed a stated number of times or at stated

intervals. A prescription containing a direction that it may be dispensed a stated number of times, but omitting direction as to the intervals at which it may be dispensed, cannot be dispensed more often than once in three days. A prescription which contains a direction that it is to be dispensed at stated intervals, but without direction as to the number of times, cannot be dispensed more than three times.

In the Rules of 1935, the Fourth Schedule occupied seven lines; the current list of Schedule Four poisons contains thirty-seven lines. This illustrates a tendency which is likely to continue and explains some of the practitioner's difficulties. In this long list, probably the seven most frequently used drugs are: the barbiturates; the sulphonamides; amphetamine and its associated compounds; the antihistamines; chlorpromazine; phenylbutazone; troxidone.

The Dangerous Drugs

These are poisons which also produce some degree of addiction. In addition therefore to being dealt with by the Dangerous Drugs Acts, they are contained also in Part I of the Poisons List and in the First Schedule to the Poisons Rules.

The purpose of the Dangerous Drugs Acts is to regulate the import, export, manufacture, sale, and use of drugs of addiction. The addiction-producing drugs are also an international problem, and developments in their use are kept under constant review by the World Health Organization.

The current Act is the Dangerous Drugs Act, 1951. Numerous regulations and orders have been made under this Act and probably will continue to be made. The principal regulations are the Dangerous Drugs Regulations, 1953.

One of the most important provisions of the Dangerous Drugs Act is that only certain specified persons are allowed to have these drugs in their possession. Doctors find a place in that group, and while many of the regulations under the Act are not of direct interest to them it is important that they should know their obligations in regard to possessing these drugs, prescribing them, and keeping records of them.

As to the possession of Dangerous Drugs, it is important for the doctor to realize that this is authorized only so far as is necessary for the practice of his profession. The continued supply of drugs to a patient solely for the gratification of addiction is not regarded as a medical need.

These drugs can be dispensed only on a prescription by a registered medical practitioner, registered dentist, or registered veterinary surgeon. The prescription must contain the particulars previously detailed in connexion with Fourth Schedule poisons. The Dangerous Drugs cannot be dispensed more than once on the same prescription unless the prescription so directs, and this is restricted to a total of three times and to the intervals specified on the prescription. Sales of Dangerous Drugs may be made directly to doctors in accordance with the Provisions of the Pharmacy and Poisons Act, 1933, as previously detailed for Schedule Four poisons.

Doctors are required to keep records of the Dangerous Drugs obtained by them and of the Dangerous Drugs supplied by them. Separate registers must be kept for these purposes and separate parts of the registers must be appropriated for each of the drugs. The entries must be made on the day in question or on the following day. The entries must give the date on which the drug was received or supplied, the amount and the form of the drug, and the authority of the person supplied to be in possession of it. However, if a doctor keeps a day-book in which he records particulars of drugs supplied by him to his patients, with the name and address of the patient and the date of supply, he may record in a separate book the date and the appropriate reference to the entry in his day-book.

It is not necessary to enter in the register of supplies particulars of drugs administered to a patient by the doctor personally or by someone acting under the direct personal supervision of the doctor.

All Dangerous Drugs must be kept in a locked receptacle. The courts do not consider a locked car to be a locked receptacle.

The authority of a doctor to possess and supply Dangerous Drugs may be withdrawn from a doctor who:

(1) has been convicted of an offence against the Dangerous Drugs Act; or

(2) has been convicted of an offence against Sections 45, 56, or 304 of the Customs and Excise Act, 1952, in respect of goods being a drug; or

(3) is the subject of a reception order under the Lunacy Act, 1890; or

(4) is the subject of an order deemed to be or having effect as if it were an order under the Lunacy Act, 1890; or

(5) is undergoing treatment as a temporary patient under Section 5 of the Medical Treatment Act, 1930; or

(6) in Scotland, is the subject of a reception and detention order, or is a voluntary boarder under the Lunacy (Scotland) Acts, 1857–1919;

and who in the Secretary of State's opinion cannot properly be allowed to remain an authorized person. Notice of the withdrawal of authority is published in the *London Gazette* and the *Edinburgh Gazette*.

The current list of Dangerous Drugs contained forty-seven items as at June 1, 1958. The most important of these are medicinal opium, morphine, heroin, Indian hemp, cocaine, pethidine, and amidone.

Antibiotics and Corticosteroids

In addition to the regulations regarding poisons and Dangerous Drugs, which have been described, Parliament has also been concerned with the control of the supply of penicillin and such other therapeutic substances as may appear to the Ministers of Health of England and Northern Ireland and the Secretary of State for Scotland after consultation with the Medical Research Council to be capable of causing danger to the health of the community if used without proper safeguards. The main legislation concerning these substances is contained in the Penicillin Act, 1947, and the Therapeutic Substances (Prevention of Misuse Act), 1953. So far as the medical profession is concerned, the principal result of these Acts and the regulations made under them is that the antibiotics and cortisone derivatives can be obtained by the general public only on a prescription signed and dated by a registered medical practitioner.

The control of poisons and Dangerous Drugs in hospital is a special subject and has recently been under investigation by a departmental committee.[2] Those who are concerned with this problem should study the report of the committee and particularly the summary of recommendations.

REFERENCES

[1] Locket, S., *Clinical Toxicology*. London, 1957.

[2] *Control of Dangerous Drugs and Poisons in Hospitals*. Report of the Joint Subcommittee, Central Health Services Council, Ministry of Health. H.M. Stationery Office, London, 1958.

The World Federation for Mental Health held its tenth annual meeting at Copenhagen last year, and the papers, together with discussion on them, have now been published as *Growing up in a Changing World* (pp. 238; 15s. net). MARGARET MEAD begins the volume with some contrasts between different cultures in the way infants are cared for, and later S. HERMANN and E. A. KRAPF discuss the work of Unesco and W.H.O. respectively in relation to mental health problems. In a section on the prevention of juvenile delinquency KENNETH SODDY (United Kingdom) draws attention to the limits within which punishment might be effective in keeping children out of delinquent ways. He added, "I think that it requires great qualities of imagination for a child to be deterred from following a delinquent whim by the thought of punishment that he may very well hope to escape." Other themes discussed include problems of puberty, genetics, refugees, and disturbed families. The volume is issued by H. K. Lewis Ltd., of London.

FIRST B.M.A. ANNUAL CLINICAL MEETING SOUTHAMPTON, DECEMBER 4-7

Last week we reported the plenary sessions and panel discussions, the Transatlantic Clinical Conference, the demonstrations of colour television and medical films, and the social events of the first two days of the first B.M.A. Annual Clinical Meeting (*Journal*, December 13, p. 1465). This week we conclude our report with an account of what happened on the last two days. A total of 325 doctors attended the meeting, which was accounted on all sides a great success. The Association plans to hold its second Annual Clinical Meeting next year at Norwich.

PANEL DISCUSSIONS

Saturday, December 6, 9.45 a.m.

Risks of Therapy

As on the Friday, Saturday began with two simultaneous and well-patronized panel discussions. The first was under the chairmanship of Dr. R. M. S. MCCONAGHEY (Dartmouth), who had with him Dr. RICHARD ASHER (London) and Mr. D. F. ELLISON NASH (London). They addressed themselves to the question of "The Risks of Therapy."

Opening the discussion, Dr. MCCONAGHEY remarked that the ancient Egyptians in their "textbooks" had recognized that certain diseases were incurable and "should not be touched." He divided risks of therapy into three kinds—risks to the patient, to the doctor, and to the community.

Dr. ASHER said that one danger to the patient was that therapy could prevent diagnosis. He had been invited to diagnose suspected cases of pernicious anaemia which had already been given vitamin B_{12}, and suspected cases of myxoedema which had been given thyroid. He couldn't do it. An opposite danger was the sudden withdrawal of a treatment which should only be withdrawn gradually, as with adrenal cortical steroids. Withdrawal of therapy could sometimes be very difficult, observed Mr. NASH. Psychiatry, once started, was often hard to stop, as was physiotherapy in cold weather when the patient was getting free transport. He thought that doctors nowadays ran more risks than patients and quoted a report that there were 5,000 complaints a year known to medical defence organizations from patients who considered they had not received proper treatment. Dr. ASHER deplored that the public had got the idea that where there was an illness there was necessarily a remedy. They thought treatments always did good and therefore everyone ought to be getting some. They got this notion from magazines. The community could almost be said to have an addiction to treatment. The unfortunate result was that the doctor gave treatment even if the patient was not ill, because it was expected; and the patient thought that, as he was being treated, he must be ill.

Tests to Impress the Coroner

Dr. K. M. ROBERTSON (Southampton) thought that risks of therapy, especially of new drugs, were overstressed in medical journals, and that this caused doctors to fear to take what should be routine risks. Doctors tended to be frightened unduly by individual catastrophes. He also suspected that hospital doctors might be engaged in trying to keep some new drugs to themselves so as to be one up on the general practitioners. Dr. ASHER retorted that, of course, the consultant must have his mysteries from other doctors—it was gamesmanship. He too thought there might be undue fear of taking risks because of the possibility of being sued. He regretted the use of tests to impress the coroner, if they did not also protect the patient. Weekly blood counts in patients taking thiouracil were an example of this.

Mr. NASH, however, did not think thiouracil a good example of a drug which might be used more freely. It could make patients myxoedematous and possessed of very vascular goitres, altogether unattractive subjects for surgery. He suggested that there was undue fear of using chloramphenicol in urinary infections. When these proved resistant to other drugs chloramphenicol should not be withheld.

On risks of therapy to the community Dr. MCCONAGHEY pointed out that diseased individuals—e.g., epileptics and imbeciles—were being preserved by medicine, and Dr. J. H. BARON (London) reminded the meeting that the population of backward countries was increasing rapidly as a result of medical advances and that this led to immense social problems. Dr. ASHER agreed, but pointed out that it would be quite impossible for a doctor not to treat individual patients, because their survival might present problems to which we could see no solution.

Dr. W. M. DIXON (Fawley) observed that we must not imagine that because drugs are prescribed they are necessarily consumed by the patient, and Dr. ASHER thought that this was an important factor in diminishing the risks of therapy. He thought medical practice was getting needlessly complicated. In his young days blood transfusion was simple. But look at it now! It was terribly complex because of alleged risks. In the old days he used to give blood quite happily.

Mr. NASH drew attention to the virtual abolition of thoracic surgeons' waiting-lists by the advent of effective chemotherapy. (The CHAIRMAN supposed that was a risk of therapy for thoracic surgeons.) Surgeons, continued Mr. NASH, had higher risks of litigation than physicians. Fear of this was not wholly bad. The surgeon must protect himself, of course, but not at the cost of terrifying his patients.

Dr. ASHER spoke of the risk of the patient's finding out what was wrong with him. Patients should not generally be told when they had a hopeless prognosis. In his experience this led to misery and distress. Hope should be given even where there were no grounds for it. Mr. NASH said his opinion and experience on this matter were exactly the reverse of Dr. Asher's.

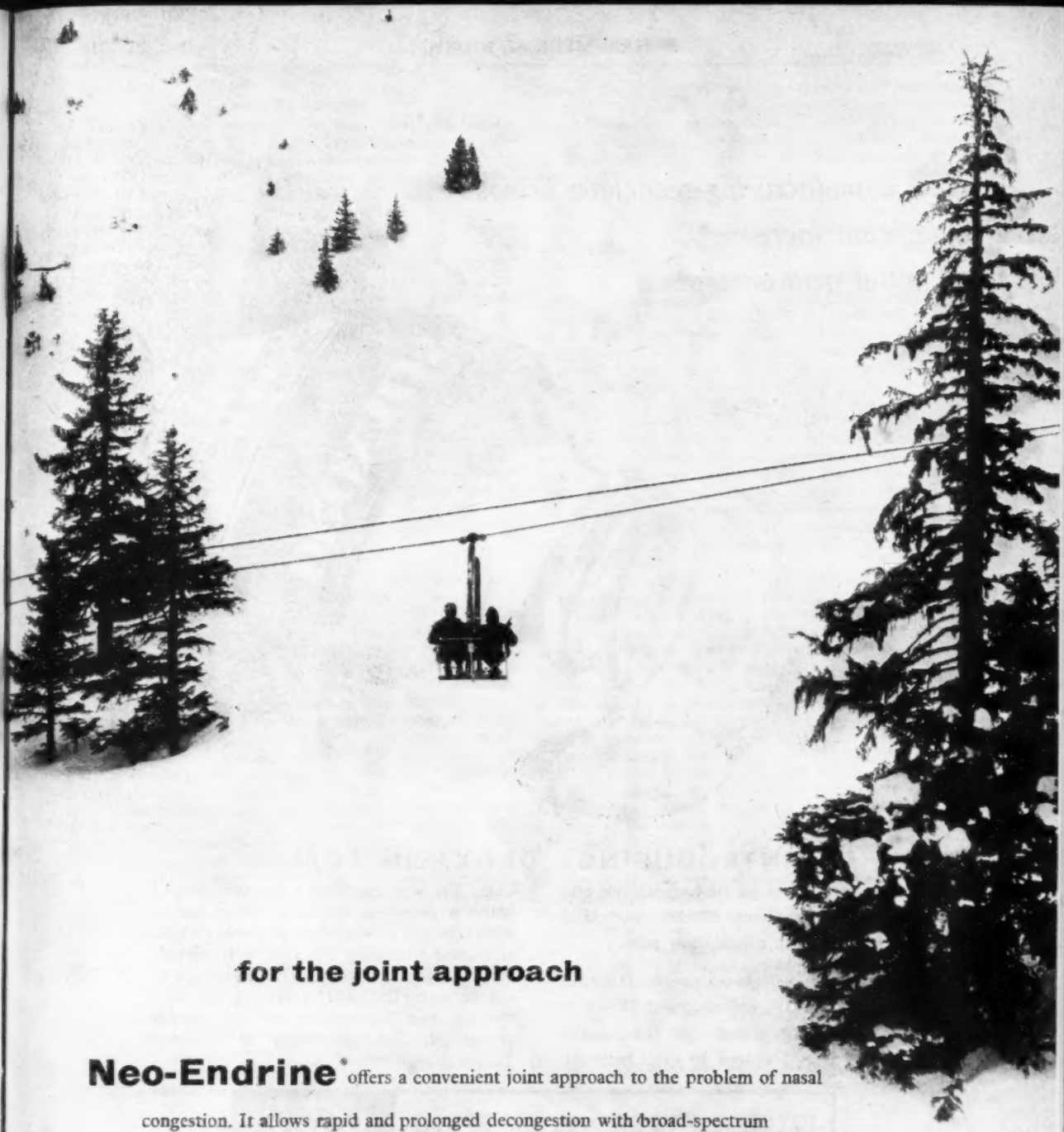
Other risks discussed were those of self-treatment by patients. Haematemesis from aspirin, renal stone from alkali treatment of peptic ulcer, and impotence from antihistamines were cited. Also the risks of quacks growing rich on patients who had been given a bad prognosis were grave: it was human nature not to give up hope, and human nature to exploit that fact. But the meeting could think of no practicable way of diverting this money to more deserving recipients.

More Geriatic Surgery Advised

Mr. R. P. M. MILES (Chichester) thought surgery in the very old often led to trouble; the patient was often "never the same man again." Mr. NASH disagreed. The more old people operated on the better. In fact they were often anaesthetized more safely, with their breathing being done for them, than they were walking about straining themselves. His advice was to get the hernia or the piles out of the way, so that they would not remain to complicate other diseases—prostatic enlargement, for example—making the patient worse off when he had to be operated upon. An efficient rehabilitation service was, of course, vital in geriatric surgery.

Dr. ASHER agreed. Old people wanted to live, or die; merely to exist in discomfort was useless to them. Surgeons should take more risks and not worry about spoiling a set of good operating figures. Dr. MCCONAGHEY said it was not surgery that did old people in, but hospitalization and being put to bed. Dr. ASHER said he could talk indefinitely about the dangers of bed. He had once even written an article on the subject.

The CHAIRMAN turned the attention of the meeting to diagnostic investigations, unnecessary use of which was condemned. Sometimes they caused more discomfort than the disease. Dr. ASHER said he would rather have pernicious anaemia than undergo a modern full-scale investigation to see if he had. Patients should be given hope and not be over-investigated, he said. But Mr. NASH repeated that they should be told the truth as well as not being over-investigated.



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Ocular Emergencies

The other panel, whose subject was ocular emergencies, consisted of Mr. B. W. RYCROFT (East Grinstead) and Mr. A. G. LEIGH (London), under the chairmanship of Mr. E. C. ZORAB (Southampton). They discussed first acute glaucoma.

Mr. RYCROFT reminded the audience that acute glaucoma was a sick eye in a sick body, and that views on its cause were changing. It had been believed to be due to interference with the drainage of fluid from the eye, but now a centre in the mid-brain was thought to be responsible for the tension of the eye. As acute glaucoma could cause very rapid blindness, prompt diagnosis and treatment were imperative. There might be gradual loss of vision or the appearance of a halo round lights. Treatment was the use of eserine drops to contract the pupil, and acetazolamide ("diamox"), 250 mg. thrice daily by mouth, or intravenously if necessary. Mr. LEIGH stressed the importance and the difficulty of the diagnosis, which rested on the recognition of a steamy cornea in a red, tender eye with a dilated pupil. The pain was so severe that it could not be accurately localized and was sometimes wrongly diagnosed as due to abdominal catastrophes, etc. Surgery had now been almost completely supplanted by acetazolamide therapy, and it was very unusual for recovery not to ensue. If acetazolamide failed, then iridectomy was necessary.

Corneal Lesions

The panel then discussed lesions of the cornea. Mr. LEIGH recalled that corneal epithelium is capable of regeneration without scar. In an abrasion some of the epithelium was wiped off; it regenerated partly by pseudopodial migration from the edges of the defect, partly by mitosis. The defect could be covered within hours, but the repair was very delicate and the slightest further injury would remove the new epithelium. Diagnosis was made by instilling 2% fluorescein, which stained the injured part. Treatment was by pad and bandage; cocaine prevented healing. Adherence of the repaired defect to the upper lid caused stripping and recurrence the next day. Antibiotic drops and atropine were then required. To prevent regurgitant infection via the lacrimal ducts, pressure should be applied to the lacrimal sac; infection of a corneal abrasion could lead to loss of the eye.

Mr. RYCROFT said that dendritic ulcer was thought to be due to a virus. It often followed an excessively high fever. Treatment was difficult owing to recurrence and scarring. Cauterization with carbolic was the first line of treatment, together with atropine, pad, and bandage; local hydrocortisone was definitely contraindicated. The condition usually lasted for three or four weeks. Mr. LEIGH said that, although some dendritic ulcers responded to cortisone, some would develop virus keratitis involving the whole cornea, so destroying sight. Mr. RYCROFT said that after one or two recurrences a deep lamellar graft was useful. Mr. ZORAB said that without a good light, magnification, and fluorescein, dendritic ulcers could easily be missed. They should be looked for in any sore eye.

Retinal Detachment

Mr. LEIGH said detachment of the retina could present as a sudden loss of vision, but usually only a shadow was noticed. Ophthalmoscopy was the only means of diagnosis, but the presence of blood might prevent a clear view. Treatment began with rest in bed. At operation diathermy was used after evacuation of the subretinal fluid. Results were improving because of the introduction of scleral resection and scleral buckling (which took only three hours to do). Mr. RYCROFT mentioned three important symptoms: a "curtain" in the field, flashes of light in one part of the field, and alteration in the quality of vision—for example, a lamp-post would have a kink in it. He suggested vitreous transplantation to push the retina back into place.

Mr. Rycroft then considered acute infections of the lids and lacrimal apparatus. A red eye was often wrongly put down to conjunctivitis, he said; the one sure sign of conjunctivitis was stickiness of the lids. Itching was often due to pinguecula, and irrigations used in the treatment of conjunctivitis usually made the irritation of pinguecula worse. Infections of the lacrimal sac in infants due to failure of canalization of the duct were treated by massage of the sac, and 95% would recover in six months. If not, then probing should be undertaken, a procedure possible at that age but more difficult later owing to the change in direction of the duct. In adults, obstruction was due to fractures or to nasal infection. Dacryocystorhinostomy was necessary. Removal of the sac was to be condemned.

Cross-examination of the Panel

Wing Commander E. H. LAMB asked how much retinal detachment made a case hopeless. Mr. LEIGH said that 60% of all cases treated were successful; but, once the macula was detached, visual acuity was never fully restored. Provided a small sector of retina remained attached, a good result could follow treatment.

Dr. J. L. STRUTHERS (Southampton) asked if corneal abrasions from vegetable matter were more serious than those caused by animal or mineral material. Mr. RYCROFT said that the most dangerous substances he had met were caterpillar hairs and cactus spikes. The danger depended upon the subsequent infection. Dr. E. GREY-TURNER (London) asked how long a recurrent corneal abrasion should be allowed to go on for. Mr. LEIGH replied that a lamellar corneal graft was the ideal treatment for the chronic case.

Asked what should put the practitioner on his guard against chronic glaucoma, Mr. RYCROFT said that a patient with failing sight should be examined by an ophthalmic surgeon and not only by an optician. An optician might ascribe the failure of sight to a small cataract, which he could see, but without dilatation of the pupil and examination of the fields the real cause of the reduced vision—namely, chronic glaucoma—could be missed. Mr. ZORAB emphasized that the painlessness of chronic glaucoma made it easily missed.

Using acetazolamide, was it permissible for a G.P. to hold an acute glaucoma for, say, eight hours? Mr. LEIGH said that, if the practitioner was able to judge the response to treatment by noting the cessation of pain, clearing of the cornea and contraction of the pupil, and diminished tension, then it was perfectly justifiable to hold such a case. Mr. ZORAB said it was now no longer necessary for the ophthalmic surgeon to get up in the middle of the night for acute glaucoma, thanks to acetazolamide, but it only gave a breathing-space. Mr. LEIGH mentioned that the chances of glaucoma starting in the second eye were very high, but tests were now available to tell in a given case if that was likely: if so, a preventive operation should be done. Mr. RYCROFT said that sedation was an important adjunct to treatment. The last question concerned vitreous haemorrhages, and Mr. LEIGH said that he found them very difficult to treat. He was doubtful if any treatment was of value.

The remarkable thing about this panel was that all three members were in agreement over everything that was said.

THIRD GENERAL SESSION

Saturday, December 6, 10.45 a.m.

As in the previous general sessions three invited speakers gave short discourses on unrelated topics. For the last of the general sessions, held under the chairmanship of Dr. I. D. GRANT (Glasgow), the speakers were Sir RUSSELL BRAIN (London), Dr. J. T. INGRAM (Leeds),* and Professor E. STENGEL (Sheffield).

Acroparaesthesiae

Sir RUSSELL BRAIN spoke on acroparaesthesiae, illustrating his observations with lantern slides. He said the term implied three things—namely, that the distal parts of one or more of the extremities were involved in a sensory

*Dr. Ingram's appointment to a new chair of dermatology at Durham University was announced last month (*Journal*, November 22, p. 1302).

disturbance which was not a mere lack of feeling but had some positive quality such as tingling which was usually of an unpleasant character. Within this definition there were different forms of acroparaesthesiae characterized by varying degrees of unpleasantness, which in severe cases amounted to pain.

In taking the history of a patient complaining of acroparaesthesiae it was important to get as full an account as possible of the quality of the abnormal feelings and of their distribution, whether the onset was related to any particular posture, whether they occurred only when the patient was lying in bed, and, if so, at what part of the night they came on. Paroxysmal acroparaesthesiae had a different pathogenesis from persistent ones. Their cause was reversible, a vascular factor probably playing an important part. If paroxysmal acroparaesthesiae became persistent, a change which for the time being at least had become irreversible must have taken place. The same was true of acroparaesthesiae which were persistent from the beginning.

All the commonest causes of acroparaesthesiae appeared to involve one or more posterior spinal roots or peripheral nerves in such a way as to lead to their direct compression or an interference with their blood supply, or both. When the pressure operated paroxysmally its effects were reversible, but if it was repeated sufficiently often, or was long-continued, pathological changes were likely to occur in a nerve root or nerve, initially oedema, and later, if the oedema was not relieved, fibrosis. Acroparaesthesiae most commonly occurred in the upper limb, where their three main causes were (1) cervical spondylosis, (2) drooping shoulders, and (3) compression of the median nerve in the carpal tunnel.

Two main types of acroparaesthesiae occurred as a result of cervical spondylosis. Involvement of a single spinal posterior root was likely to cause pain, tingling, and numbness within its cutaneous distribution, which was worse if the patient lay on the affected side in bed, and the numbness was usually constantly present. The other type of acroparaesthesiae consisted of more widespread sensations of painful tingling, numbness, stiffness, and swelling often involving the whole hand. These tended to awaken the patient at night after a few hours' sleep. The acroparaesthesiae associated with drooping shoulders were usually more troublesome during the day than at night, and were specially prone to affect the inner border of the forearm and hand. The low position of the shoulders was evident on examination, especially from behind, and a lateral radiograph of the cervical spine gave a clear view of the body of the first and often, also, the second dorsal vertebra.

When the median nerve was compressed in the carpal tunnel the acroparaesthesiae had the characteristic distribution of the sensory supply of the nerve to the thumb, index, middle finger, and radial side of the ring finger. These acroparaesthesiae were also prone to awaken the patient at night. They soon became associated with objective sensory loss over cutaneous areas of the digits supplied by the median nerve and some wasting and weakness of the outer thenar muscles. Pregnancy sometimes led to acroparaesthesiae arising from either the cervical spine or roots or, less often, the median nerve.

In the lower limb the sensory disturbances in meralgia paraesthetica were not strictly acroparaesthesiae, though they had a similar quality and pathogenesis.

All these benign sensory symptoms needed to be distinguished from paraesthesiae produced by organic disease of the spinal cord, especially disseminated sclerosis, subacute combined degeneration, and atheromatous ischaemia, and from disorders of cerebral origin.

Sir RUSSELL BRAIN, in reply to questions, suggested that rest gave most relief for acroparaesthesiae of pregnancy; there was no specific treatment. Pain from the carpal tunnel syndrome would sometimes affect the arm even to the shoulder. Exceptionally it was possible to have symptoms from cervical spondylosis with normal radiographs. This was due to a moving intervertebral disk. Manipulation of the cervical spine, after heat and without an anaesthetic, might give relief if there was muscle spasm.

"The Restless Skin"

In discussing "The Restless Skin," Dr. JOHN T. INGRAM (Leeds) said it was important for every practitioner to recognize the essentially dynamic nature of the skin. Too often the skin was regarded as something static. Our ideas derived from impressions gained from examining dead material under the microscope. The skin was not an inert envelope enclosing the living organism; it was at least as vital as other parts, if not more vital than most. It certainly participated in and commonly reflected all types of systemic activity, as, for example, the metabolic, endocrine, vascular, and emotional. It was rather like a vast sea, with its unfathomable depths resting upon an unseen bed which might influence its behaviour or erupt to the surface; in addition the surface waters independently might evolve mischievous antics of their own.

These inherent activities, which concerned all the elements of dermis, epidermis, and appendages, often working in harmony, constituted the communications of the individual with the world at large, his life. If we visualized this organ caressed by vascular elements and fine nerve fibrils, it was not difficult to be aware of the restlessness of the skin, and of the significance—and the value and danger—of that restlessness. Injury to the skin and the resulting lesion were important, but we tended to note the insult and too often forgot the sensitive patient and the immediate circumstances.

In local treatment it was rarely necessary to depart from the time-honoured and effective applications that were bland, non-irritating, and non-sensitizing, provided they were dispensed properly and applied properly. The services of a nurse were invaluable.

Where a persistent eruption was limited in extent, the doctor must never tire of seeking a local sensitizing contact. He should not be content with the label allergic unless prepared to find the allergen. Whatever the aetiological balance, however, it was always profitable, from the start, to help to restore general and dermatological calm by prescribing sedatives internally.

In reply to questions, Dr. INGRAM agreed that upon occasion effective treatment of a skin lesion might upset a patient physically or mentally. This was not likely to happen if treatment was directed to the whole patient in relation to his whole environment. He said that applications of hydrocortisone lotions and creams were of particular value in local, irritable, and eczematous affections such as otitis externa, affections of eyelids, and pruritus of the genital and anal regions. They were not of such value in thickened lesions or in widespread eruptions, which was perhaps fortunate, since hydrocortisone was so expensive. Asked about endocrine therapy in acne vulgaris, he said that, though endocrine factors clearly played an important role in its aetiology, treatment with hormones was unsatisfactory and sometimes harmful. Occasionally small doses of oestrogens helped girls, but they were not effective in boys. Gonadotropins had proved disappointing.

Suicide and Attempted Suicide

Professor E. STENGEL (Sheffield) said that there were many common misconceptions about suicide and attempted suicide. It was wrong to believe that people who threatened suicide would not do it. In fact many gave a warning of their intentions, thus allowing their "environment" to intervene.

Attempted suicide was not necessarily unsuccessful suicide; there were not two grades of suicide, the successful and the unsuccessful. That notion presumed that the only motive for the suicidal act was self-destruction. Like most human behaviour the suicidal act reflected the conflict between love and hate—the contact-seeking tendencies on the one hand and the destructive tendencies on the other. The outcome of the suicidal act depended largely on the relative strength of these tendencies. It was generally thought that the outcome of the act depended mainly on the method employed and the

seriousness of the intent. But it also depended on the reaction of the environment and on other imponderable factors. Suicidal acts had the character of a gamble, or rather of an ordeal.

Follow-up studies showed that people who commit suicide and those who attempt suicide form two different though overlapping populations. Only a small proportion of those who attempted suicide killed themselves and only a minority of those who killed themselves had attempted suicide before. Nevertheless the likelihood of suicide amongst those who had attempted it was much greater than in the general population. Suicidal acts were much more frequent in older people than in the young, contrary to a commonly held opinion; and poverty was not an important factor. Depressive illness carried the most serious risk of suicide.

Legislation against those who attempted suicide was a cause of much distress. The incidence of suicide was lower in Scotland, where suicide was not a criminal offence.

In discussion Professor STENGEL agreed that the motive was sometimes veiled aggression, the desire to inflict punishment on others. Considering the incidence of suicide in different Scandinavian countries he felt that prosperity, alcoholism, and industrialization were important influences. The social code of various classes differed and there was often a fear of decline in status. He did not think that referring a depressive patient to hospital was likely to cause attempted suicide; the patient was the best witness to that.

HOSPITAL DEMONSTRATIONS

The afternoon of Saturday was devoted to clinical demonstrations in the various departments of the Southampton hospitals. The demonstrations were illustrated by slides, diagrams, charts, and photographs on whose preparation a great deal of care and hard work had been expended. At the *Southampton General Hospital* thyroid disease was discussed by the physicians, and Crohn's disease in the Surgical Department. A full programme, largely devoted to the general-practitioner aspects of midwifery, was given in the Department of Obstetrics and Gynaecology; whilst the neurologists demonstrated the result of treatment of intracranial angiomata. Members of the Department of Anaesthetics discussed some problems of respiratory insufficiency and presented a case of tetanus under treatment in the Respiratory Unit. The problem of nursing the elderly, the treatment of deafness, and speech training after laryngectomy, as well as demonstrations of laboratory techniques in the Pathological Department, and a film on swallowing in the Department of Radiology, were other items on the programme.

At the *Royal South Hants Hospital*, besides clinical demonstrations in the Departments of Medicine and Surgery on endocarditis and peripheral vascular disease, respectively, the orthopaedic surgeons, the pathologists, and the physiotherapists all discussed problems arising in their specialties. The new rotating caesium telecurie treatment unit was also on show. Particularly well attended sessions were held by the dermatologists and the paediatricians.

At *Southampton Chest Hospital* cases were demonstrated to small groups of visitors, and aspects of thoracic surgery, cardiology, and thoracic medicine were discussed at the bedside. A film on closure of an atrial septal defect under hypothermia was shown. The Department of Anaesthetics held a discussion on the anaesthetist's role in thoracic surgery. The continuous demonstration at the *Southampton Eye Hospital*, which was limited to 30 visitors, was fully attended. The examination and discussion of patients with various ophthalmic conditions were carried out in small groups, and after this three films were shown.

SUNDAY VISITS

On Sunday morning visits were made to five centres of interest in the vicinity. Visitors to the Department of Daily Living at the *Royal Hampshire County Hospital* at Winchester had the opportunity of first attending Matins in Winchester Cathedral, where places had been reserved for them in the choir. After this Dr. W. RUSSELL GRANT gave a fascinating demonstration of ingenious and simple gadgets and adaptations to the home, whereby those afflicted by disease or injury can lead an active life despite their disabilities. At *Odstock Hospital, Salisbury*, in the Department of Physical Medicine and Plastic Surgery, Dr. HUGH J. GLANVILLE and Mr. J. N. BARRON discoursed on treatment and subsequent rehabilitation after acute injury. This was followed by a visit to the Nuffield Department of Rehabilitation, where patients were seen regaining their working capacity on modified and adapted machinery.

Both these demonstrations at Winchester and Odstock were followed by receptions given by the local Divisions of the B.M.A.

Another party visited the *Veterinary Artificial Insemination Centre* of the Hampshire Cattle Breeders' Society at Lyndhurst. The laboratory work undertaken in solving problems of breeding, cross-breeding, fertility, and the treatment and storage of semen was described. Mr. K. G. ELCOATE and Mr. D. H. MADDON included in their demonstration a visit to the bull pens, where semen was collected, and discussed some of the practical problems involved in artificial insemination.

A number of visitors made a tour of the *Port of Southampton*, where after visits to the King George V Graving Dock and the Ocean Terminal Dr. W. P. CARGILL gave a talk on some of the medical problems of a great port. Finally a party were shown round the vast *Esso Refinery at Fawley*, where Mr. COLIN SOUTHALL conducted the visitors on a tour of the various plants. Dr. A. WARD GARDNER described the special problems met with by the Medical Department, and took the party to see the new hospital wing of the Refinery, which is in his charge.

APPROVED NAMES

The last supplement to the consolidated list of "approved names" was published in the *Journal* of September 20 (p. 739). A new supplement, dated December, 1958, is printed below. Communications relating to "approved names" should be addressed to the secretary, British Pharmacopoeia Commission, General Medical Council, 44, Hallam Street, London, W.1.

Approved Name	Chemical and Other Names	Notes
Anisindione ..	2-*p*-Methoxyphenylindane-1 : 3-dione "Miradon"	Anticoagulant
Cloquinate ..	Chloroquine di-(8-hydroxy-7-iodo-quinoline-5-sulphonate) "Resotren"	Amoebicide
Dieldrin ..	Product containing 85% of 1 : 2 : 3 : 4 : 10 : 10-hexachloro-6 : 7-epoxy-1 : 4 : 4*a* : 5 : 6 : 7 : 8 : 8*a*-octa-hydro-*exo*-1 : 4-*endo*-5 : 8-dimethano-naphthalene	Insecticide
Halopenium chloride	4-Bromobenzyl-3-(4-chloro-5-methyl-2-*iso*propylphenoxy)-propyl-dimethylammonium chloride	Antibacterial and antifungal agent
Isopropamide iodide	(3-Carbamoyl-3 : 3-diphenylpropyl)-methyldi*iso*propylammonium iodide "Darbid"; "tyrimide"	Anticholinergic agent
Mestanolone ..	17β-Hydroxy-17-methyl-5α-androstan-3-one "Androstalone"	Protein anabolizing hormone
Methsuximide	*N*α-Dimethyl-α-phenylsuccinimide "Celontin"	Anticonvulsant
Noscapine ..	Narcotine "Coscopin"; "nicolane"	Antitussive
Poldine ..	2-Benziloyloxymethyl-1-methylpyrrolidine "Nacton" is the methosulphate	Treatment of peptic ulcer
Prampine ..	*O*-Propionylatropine "PAMN" is the methonitrate	Anticholinergic agent
Promethazine theoclate	*N*-(2-Dimethylamino-*n*-propyl)phenothiazine salt of 8-chlorotheophylline Promethazine chlorotheophyllinate "Avomine"	Antihistamine
Sulphamethoxypyridazine	3-*p*-Aminobenzenesulphonamido-6-methoxypyridazine "Kynex"; "lederkyn"; "midicel"	Sulphonamide
Sulphatolamide	*p*-Aminobenzenesulphonylthiourea salt of *p*-sulphamoylbenzylamine "Marbadal C"	"

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Tabs. ethinyloestradiol *B.P.*
Estigyn (British Drug Houses).
Eticyclin (Ciba).
Lynoral (Organon).

Ethinyloestradiol, a semi-synthetic oestrogen, is the most potent oral oestrogen, being about 20–25 times as active as stilboestrol, but costing more. The justification for the higher cost would be a smaller incidence of intolerance than is shown to stilboestrol; unfortunately this is by no means certainly the case. The indications for ethinyloestradiol are the same as those for other oestrogens: replacement therapy in hypo-ovarianism (dose about 0.1 mg. daily in 20-day interrupted courses) and in the climacteric (about 0.01 mg. or less daily, again in interrupted courses); treatment of menstrual irregularities of functional origin (daily dose about 0.1 mg.); suppression of lactation (no two people seem to have the same views on the precise regime for this, so it probably does not matter); and palliative treatment of prostatic carcinoma (daily dose 0.1 mg. and upwards, according to clinical response), and of some post-menopausal patients with carcinoma of the breast.

In general, it may be said that if stilboestrol is tolerated in doses which are adequate for the purpose there is no reason to use any other oestrogen; if it is not, ethinyloestradiol in equivalent dosage may be tried. Some patients will tolerate it better, but others will not.

N.H.S. basic price: all preparations, 0.01-mg. tablets or linguets (eticyclin), 100 for 1s. 6d.

Injection of cyanocobalamin *B.P.*
Anacobin (British Drug Houses).
Bitevan (Evans Medical Supplies).
Cobalin (Paines and Byrne).
Cobastab (Boots).
Cytamen (Glaxo).
Distivit B_{12} (Distillers).
Duodecibin (Woolley).
Fermin (Richter).
Megalovel (Vitamins Ltd.).
Rubramin (Squibb).

Cyanocobalamin is of greatest value in the treatment of pernicious anaemia. In this disease there is a deficiency of it, so that instead of the normoblastic maturation in the bone marrow leading to the formation of normal red blood cells a megaloblastic reaction occurs, and pernicious anaemia develops. This faulty marrow response is corrected within a few days of adequate treatment with cyanocobalamin parenterally. It may be given in doses of: (1) initially, 250 μg. for two or three days in the first week, followed by 250 μg. twice weekly until the blood count is normal and symptoms of posterolateral sclerosis are minimal; then only should the dosage be reduced gradually until (2) a maintenance dose is reached, which may vary in different patients but is usually about 100–250 μg. weekly and then fortnightly. It is usually undesirable for prolonged maintenance therapy to be so infrequent as 50–100 μg. at monthly intervals. Some cases of tropical macrocytic anaemia and a few cases of sprue respond to treatment with cyanocobalamin.

N.H.S. basic price:—Six 1-ml. ampoules for injection, each containing 100 μg. cyanocobalamin: inj. cyanocobalamin. *B.P.*, 2s. 7½d.; anacobin, 2s. 7½d.; bitevan, 2s. 7½d., cobalin, 2s. 8d.; cobastab "viules," 2s. 7½d.; cytamen, 2s. 7½d.; duodecibin, 3s. 4½d.; fermin, 3s. 4d. Five 1-ml. ampoules of 100 μg.: distivit B_{12}, 2s. 2d.; megalovel, 2s. 6d. Rubramin, 5-ml. vial of 100 μg., 2s. 8d. Ampoules containing doses of different sizes are available.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

B.M.A. Clinical Meeting

SIR, — "Never a dull moment" — that is how a Southampton colleague described the B.M.A. Clinical Meeting as we came through the swing-doors of the Guildhall after the final general session. What a busy and enlightening experience the three days' meetings have been, especially for a member of an antipodean Branch, as I am.

From such a wealth of splendidly presented items it is hard to select any for special comment, and anyway individual tastes and interests differ. The colour televising of surgical operations from the Southampton General Hospital, the Transatlantic Clinical Conference, the clinical demonstrations at the hospitals—all were evidence of superb planning. And there was so much more.

The Annual Clinical Meeting has been well launched. Developing from this initial triumph, succeeding meetings in years to come will do much to assure the continued advancement of British medicine. All who contributed to this 1958 success have reason to be proud.—I am, etc.,

Adelaide, South Australia. A. R. SOUTHWOOD.

Antibiotics in Acute Tonsillitis and Otitis Media

SIR,—I must take issue with Dr. Peter A. Walford (*Journal*, November 29, p. 1353) on this subject. To say that the rarity of rheumatic fever warrants the withholding of antibiotics in sore throats is as illogical as to say that because diphtheria is also so rare there is no point in continuing immunization. Incidentally I have yet to hear that the decline in diphtheria is attributed to a waning in virulence of the causative organism. Penicillin is just as specific a therapy for streptococcal sore throat as immunization is a specific prophylactic for diphtheria.

Since it is not refuted that acute nephritis and rheumatic fever follow streptococcal infections, it is logical to treat such infections as early as possible with the specific remedy. To withhold antibiotics for 24 to 48 hours, as Dr. John Fry did in his series of cases (*Journal*, October 11, p. 883), cannot, to my mind, give a true comparison between treated and untreated cases. The most striking results with penicillin in acute tonsillitis and otitis media are observed when the antibiotic is administered early in the infection, as is so often possible in general practice. Dr. Walford quotes a paper by Wilson[1] written in 1946, showing that after penicillin therapy there was some degree of hearing loss in 18% of his series of cases. However, the doses in use at that time would hardly be considered adequate by present-day standards. A more recent survey by Dixon[2] has shown that, in 114 otitis media infections treated with penicillin without myringotomy, there were only four cases of minimal hearing loss and there were no complications. The author concludes that this is a highly satisfactory result.

Dr. Walford asks for other practitioners' experiences of the incidence of acute nephritis and rheumatic fever. I can only say that in my own practice over eleven years (during which time I have used antibiotics extensively) I have seen no cases of either condition.—I am, etc.,

Twickenham. DAVID WHEATLEY.

REFERENCES
[1] Wilson, C. P., *J. Laryng.*, 1946, **61**, 404.
[2] Dixon J. W., *ibid.*, 1958, **72**, 227.

Resistant Staphylococci

SIR,—Dr. Mary Barber and her colleagues are to be congratulated on their efforts to clarify the problems associated with antibiotic-resistant staphylococcal infections (*Journal*, December 6, p. 1377). There are, however, two points on which further clarification might be possible.

The first concerns the emergence of erythromycin-resistant strains. There is strong evidence implicating group III staphylococci as the principal offenders. The question remains, however, as to what extent the level and duration of erythromycin administration affected the outcome. Is it possible to compare the treatment of those patients infected with group III organisms and who did not eventually produce resistant organisms with the treatment of a similar group from whom resistant strains were isolated? This point is of particular importance, since erythromycin is probably the least toxic antibiotic in general use at the present time, and therefore increased dosage might be employed if it can be shown that such would prevent resistant strains developing.

My second point relates to their statement that ristocetin (trade name "spontin") has serious toxic effects, "particularly on the eighth nerve." Although this drug has undergone extensive clinical trial, and is used in day-to-day practice in the U.S.A., experience in this country is very limited. To my knowledge, out of several thousands of patients treated with ristocetin, there have been only two instances of deafness, and in neither case could it be definitely stated that the deafness was due to this drug, as other antibiotics were being currently used. If Dr. Barber has additional evidence on this point, I should be most grateful to hear of it.—I am, etc.,

Abbott Laboratories Ltd., London, W.1. R. F. CRAMPTON.

Hula-hoop Syndrome

SIR,—In recent weeks I have seen an unusual number of children and young adults complaining of pain at the side of the neck associated with a pain in the upper abdomen. Both were aggravated by movement, and in the case of the neck pain it was severe enough to produce torticollis in a few. On examination, there was a varying degree of reduced movement of the cervical spine, especially of rotation, which was limited by pain, and there was spasm and tenderness in one or both sternomastoids, the cervical portion of the trapezius, and the paravertebral muscles in the cervical region. Abdominal examination revealed tenderness in the epigastric region and immediately below the costal margin. Pain was also produced in this region by straight-leg raising.

Having noticed the present fashion of the hula hoop in this area I started making inquiries from the parents of the sufferers, and so far in each case the attack followed a first indulgence in this sport.

My diagnosis was confirmed the other day when a lady of 68 presented herself with this classical picture. Whilst thinking of a possible alternative diagnosis I made the remark that had she been a little younger I would have asked her whether she had been hula-hooping yesterday. To my surprise she replied, "As a matter of fact I did have a go yesterday at young Willie's birthday party."—I am, etc.,

Stevenage. J. O. NEWMAN.

SIR,—The widespread popularity of the pastime recently introduced to this side of the Atlantic from America prompts me to report briefly the following case history.

A girl aged 7 years complained of feeling off colour and some frequency of micturition on November 28. By November 30 the frequency had gone, but she complained of pains all over and could not walk. When seen on December 1 her temperature was 102° F. (38.9° C.). Normally a very active child, she lay perfectly still in the bed. She had moderate neck rigidity, was unable to sit up unsupported, and her lower-limb movements were slow and painful. Her lower-limb tendon reflexes were diminished, but skin reflexes were normal. Her back muscles were tender especially in the mid-dorsal region.

She was admitted to hospital as a possible case of poliomyelitis. In hospital she was provisionally diagnosed as a case of benign lymphocytic meningitis. Both these were proved wrong by a normal cerebrospinal fluid, pathological centrifuged deposit in the urine, and a rapid recovery by the patient.

The reason for the "meningeal" signs was that the patient was given a hula hoop on November 29 and proved to be very proficient with it, at both neck and waist level. It is tempting to postulate that the waist level activity may have converted a cystitis into a pyelitis.—I am, etc.,

Castleknock, Co. Dublin. HALDANE G. NELSON.

Potassium Perchlorate Sensitivity

SIR,—We thought that there might be some general interest in what appears to be an unusual case of potassium perchlorate sensitivity.

In 1952 Wyngaarden *et al.*[1] demonstrated the inhibitory action of this drug on thyroid function. Since then it has been used effectively in the treatment of hyperthyroidism with minimal toxic reactions. Morgans and Trotter[2] treated 198 cases for periods of one to ten months, the side-effects noted being gastro-intestinal irritation in two patients. Godley and Stanbury[3] treated 24 patients with doses between 600 mg. and 1,200 mg. daily with good effect. Perforation of a duodenal ulcer occurred in one patient whilst on potassium perchlorate and a further patient developed dyspeptic symptoms, but no other side-effects were seen. Smellie[4] treated six thyrotoxic children effectively with the same drug and no side-effects occurred. In the case reported here potassium perchlorate appears to have been responsible for a drug reaction.

Mr. L. P., aged 37 years, first attended at our clinic on June 24 this year, when a diagnosis of moderate thyrotoxicosis was made on clinical examination. Treatment was begun with potassium perchlorate, 300 mg. thrice daily, with the intention of proceeding to thyroidectomy later. On July 14 he began to feel unwell and developed some bowel frequency. On the same evening he felt tight about the throat, had swellings on his neck, and an extensive macular rash. He was admitted to another hospital on July 17, when he was found to have a partially confluent macular rash over the whole of his body and a generalized, fleshy lymphadenopathy. A soft spleen could be felt about an inch (2.5 cm.) below the costal margin, and his throat and mouth were raw, with small areas of superficial ulceration. Apart from a pyrexia of 103° F. (39.4° C.), there were no other abnormal findings in a systematic general examination.

The rash began to desquamate and his temperature remained between 101 and 103° F. (38.9–39.4° C.) for four days, but then settled. On the tenth day after admission it rose again to 100° F. (37.8° C.) and reached this daily during the following week. Simultaneously he became oedematous in his arms, legs, and scrotum; and the skin of these regions became very fiery. Slowly the desquamation ceased and the other conditions settled.

Laboratory results were as follows: Paul–Bunnell test was negative. White cell count varied between 3,600 and 6,600/c.mm., with slight neutrophilia. E.S.R. 2 mm. in one hour. Stools showed no pathogens. Urine was normal. Serum proteins were 4.8 g./100 ml., with normal electrophoresis.

A skin test (superficial) with potassium perchlorate solution gave a positive vesicular eruption.

This man, therefore, seems to have exhibited an unusual sensitivity to this apparently innocuous drug.—We are, etc.,

New End Hospital, London, N.W.3. B. J. FAIRHURST.
A. L. M. HOLLINGWORTH.

REFERENCES

1 Wyngaarden, J. B., Stanbury, J. B., and Rapp, B., *Endocrinology*, 1952, 52, 568.
2 Morgans, M. E., and Trotter, W. R., *Lancet*, 1954, 1, 749.
3 Godley, A. F., and Stanbury, J. B., *J. clin. Endocr.*, 1954, 14, 70.
4 Smellie, J. M., *Lancet*, 1957, 2, 1035.

Prevention of Lung Cancer

SIR,—It seems clear that those doctors who refer cases of carcinoma of the bronchus in heavy cigarette-smokers to the coroner do so in the hope that the general public will be warned of the danger of the habit. Such notifications are perfectly proper, but it appears that some coroners do not know what should be done. Thus, Dr. Ian Milne, one of the coroners for the County of London, held an inquest on such a case, in which a verdict of "natural death" was returned. Dr. Milne now writes (*Journal*, November 22, p. 1292) to say that "A verdict of accidental death is, clearly, inappropriate where the incidents are repetitive,

frequent, and undated, as in the case of the cigarette addict." But, as Dr. J. Shackleton Bailey points out on the same page, Sir Bentley Purchase recorded a verdict of "accidental death" in the case of a man who died of multiple skin carcinomata, after working with arsenical sheep dip for 40 years: here the incidents must have been repetitive, frequent, and undated.

These divergent views seem to support Dr. G. B. Forbes's doubts (November 1, p. 1104) as to whether the coroner's court is the proper platform for propaganda. Indeed, if doctors acquired the habit of referring similar cases to coroners, there might be some very comical results. One can imagine a conscientious practitioner referring a case of carcinoma of the penis to the coroner, stating that it was due to a persistent prepuce. It might then be difficult for an inquest verdict to avoid stating that the death was due to inattention in infancy, although, doubtless, the negligent parents will have passed out of the jurisdiction of earthly tribunals. Again, one can imagine a death certificate which stated that the immediate cause of death was carcinoma of the cervix, due to multiparity due to careless copulation. Could the (probably) ignorant husband be charged with having caused his wife's death? Such cases are just as silly as were the manslaughter charges against Christian Scientists and other anti-medical cranks. It is indisputable that an anti-smoking campaign is overdue, but it is equally certain that coroners, many of whom are not doctors, are among the least suitable propagandists.—I am, etc.,

London, W.1. A. PINEY.

SIR,—We are grateful to Dr. R. Ian Milne (*Journal*, November 22, p. 1292) for confirming our view that a doctor who believes his patient has died from cancer of the lung, due to smoking, has the legal right to assert this belief on the death certificate, provided he is prepared to testify to this knowledge and belief on oath, and listen to contrary evidence in court. We also believe it is an ethical duty to do so.

We should like to clarify what we meant in our original letter (*Journal*, October 18, p. 980) by "in the appropriate case." Of the three main types of bronchial carcinoma, one, the adenocarcinoma, has no proved association with smoking and therefore we would not incriminate it, even if the patient were a heavy smoker. In the oat-cell or squamous type we would state that it was "due to smoking" only if there were no occupational risk from asbestos, arsenic, chromates, nickel or coal distillation. The elimination of these groups, however, would still leave the vast bulk—at least four-fifths—as being attributable. While clearly it is better to know beforehand the nature of the growth, lack of this knowledge need not prevent certification of a lung cancer death as due to smoking, for the coroner can order a post-mortem examination, as a result of which the exact histology would be established.

Atmospheric pollution is the other factor which can reasonably be incriminated, but the gross sex differences in incidence and the small variation between deaths in non-smokers in town and country strongly suggest that its role is not a major one nor comparable in importance to that of cigarette-smoking. In the heavy smoker with an oat-cell or squamous growth who has no particular occupational risk, it is reasonable to attribute the development of lung cancer to cigarettes. We consider it not only reasonable but necessary in the public interest to say so.

One further point requires attention—the feelings of the relatives of the dead patient. Naturally, due consideration should be given to these, and it is necessary to warn the relatives that the coroner may decide to have a post-mortem examination and an inquest may follow. Some will be upset; others will no doubt welcome the opportunity to establish the truth; but in neither case should their attitude be a factor which influences what the doctor will do as regards the death certificate; this has to be completed in accordance with the facts as he understands them to the best of his knowledge and belief.

Finally, we should like to endorse the view put forward by Dr. H. J. Pratap (*Journal*, November 8, p. 1165) that the psychiatric approach as to why people smoke is of prime importance. More attention will have to be given to helping those who wish to give up smoking; for this we must obtain more information and study the various aetiological factors in their social context.—We are, etc.,

Stanmore, Middlesex. NORMAN MACDONALD.
London, W.1. WILFRED LESTER.

SIR,—With respect to Dr. R. Ian Milne I do not think his letter (*Journal*, November 22, p. 1292) has altogether explained the logic of his quarrel with a doctor's use of the term "excessive" in relation to a smoking habit of 40 or 50 cigarettes a day. His objection to the term on a death certificate appears to be that it has no legal significance because it only amounts to a reason for the doctor's opinion that death from carcinoma of the bronchus was due to smoking. But surely we cannot omit consideration of degree where it is the determining factor in a cause of death. "Excessive" here is the operative word, and it would have been implied even if it had not been used at all. One might more easily sustain an objection to the word on the grounds that it was redundant. Obviously for heroin, alcohol, barbiturates, or radiation to cause death they must have been met with in excess of a safe amount whether this was over a long period or in the nature of a single lethal dose.

One cannot but agree with Dr. Milne that it was unfortunate that the use of the word "excessive" by the certifying doctor was trailed as a red herring across a case that has raised the really important question of the legal recognition of smoking as a cause of "accidental death." This especially when the medical evidence relating to causation was as conclusive as it is likely to be in any case of carcinoma of the bronchus until the correlation of smoking and cancer is less dependent upon statistical data. As I pointed out in my own letter printed below that of Dr. Milne, the real difficulty is that, whereas this correlation approaches something like certainty in the mass, the significance of the smoking habit in any specific death is entirely a question of probability based upon the excessiveness and nature of the indulgence in that instance. Whilst one could not quarrel with the opinion that 40 or 50 cigarettes a day were causative, what is one going to do about 20 or 30 or less? Similarly, where does the degree of probability cease to be significant in relation to pipe- or cigar-smoking?

Coroners are accustomed to accepting a balance of probability, as illustrated in my letter (*Journal*, November 22, p. 1293) by the case in which Sir Bentley Purchase returned a verdict of "accidental death" with no more than a statistical probability to prove that prolonged exposure to arsenic had been a cause of death from cancer. The exposure here of 40 years could be considered excessive by any standard, although I have no doubt that Sir Bentley appreciates how awkward it would be to be called upon to state exactly how many years less than 40 he would have been prepared to accept as sufficient to justify his verdict. Fortunately we medical coroners when in difficulties of that sort can always fall back upon the legal element in our calling which allows of a purely intuitive wisdom that cannot be questioned in this way. Nevertheless one does wonder when the increasing pressure of science and statistics will compel a more scientific and uniform outlook amongst us all.

Even in cases where contributory causes of death can be stated in terms of statistical probability there still remains the decision as to what degree of probability should suffice. One can hardly be content with the coroner's hunch as to what amounts to excessive exposure to arsenic, smoke, or radiation, even if he is well advised and versed in the general and particular scientific evidence relating to the case. Surely it is time that some official decision was taken in relation to death from diseases such as cancer and leukaemia which can be attributed at all to exposure to harmful environmental factors. This is not a purely academic matter with no practical significance. In the meantime, whilst it is bound to become more confused under the purely arbitrary authority that exists at present, I rather join with your third

correspondent, Mr. Leslie J. Temple (*Journal*, November 22, p. 1293), in hoping that, at least in cases where really excessive smoking has preceded cancer of the lung, we shall have some verdicts of "accidental death." Then, as usual in this country, pressure will come from the public and eventually official inquiry and guidance might lead to a wiser and more orderly attitude to this smoke menace to life and health.—I am, etc.,

J. SHACKLETON BAILEY,
H.M. Coroner, County of Norfolk (Diss District).

Medicine on Television

SIR,—Professor Roger Warwick's interesting letter about medical television programmes (*Journal*, November 29, p. 1354) draws attention to what is really a very important subject. Television, like radio, reaches a vast audience and its influence on the general public is tremendous, and is bound to become even greater in the future, whether we like it or not. It is therefore most important that both we of the medical profession and the B.B.C. make up our minds as soon as possible how future television programmes of this nature are to be handled. Discussions such as the one at the College of Surgeons recently (*Journal*, November 29, p. 1351) are merely scratching the surface of the problem.

What is needed is a proper committee appointed by the B.M.A. to thrash it out thoroughly and recommend a policy for the guidance of the producers. If properly handled it could be a golden opportunity for us to educate the public in health matters and help them to take a more sensible attitude to physical fitness and the prevention of disease. At present hypochondriasis is so widespread that it is almost universal. Patients are morbidly fascinated by disease and seem pathetically ignorant about how to keep themselves healthy. And why? Because they have never been educated in the simple elementary facts of healthy living.

If these future programmes concentrate too much on disease and not enough on health they will inevitably do harm. Cynics have dubbed the N.H.S. the National Disease Service—and with good cause; for we still devote most of our energies to curative medicine instead of adopting the more positive attitude that disease can and should be prevented by healthy living.

It must be confessed the recent pronouncement of Sir Ian Jacob that the B.B.C. has no intention of elevating its present standards and means to continue providing light entertainment most of the time is not very encouraging. Are the ideals of culture and education now to be taboo to the B.B.C.? If so, as a citizen I protest, and as a doctor I see little hope for future medical programmes. The hours of dreary drivel churned out by the B.B.C. sound programmes every day are the despair of those of us who like something interesting to listen to. Let us hope that the television will at least try to rise above such puerile mediocrity and not pander to those who merely look for sensationalism and gruesomeness in the future when medical subjects are being dealt with.—I am, etc.,

Merioneth. CLAUD C. M. WATSON.

Fishbone Furunculosis

SIR,—In the *Journal* of October 18 (p. 978) Dr. Ian Martin-Scott referred to Dr. Peter Cook's letter regarding "fishbone furunculosis" (*Journal*, September 27, p. 797) and wondered if the condition described might be an atypical erysipeloid. May I add to this interesting discussion that many North American fishermen themselves recognize two distinct clinical entities?—(1) the furunculosis type of infection, which they call "Bait Sores," and (2) the erysipeloid type, which they call "Seal Finger," "Red-fish Finger," or "Mackerel Finger," because this type is more frequently seen in seal-hunters, bait fishermen using frozen mackerel bait, or fishermen or fish-handlers who prick their fingers on Red-fish bones.

The experienced port surgeon can usually clear up the furunculosis type quickly and then concentrate on the erysipeloid. A streptococcal secondary infection causing pronounced lymphangitis and axillary adenitis is not uncommon in the "Bait Sore" type of infection, but rather rare in the erysipeloid.

The "Bait Sore" type, like basal-celled carcinoma, is quite easy to handle when superficial, but when it invades bone it is rapidly destructive. In the days when fishing schooners did not have engines, a Banks fisherman making port against a head wind would sometimes bring in a man with a late furunculosis type of infection which had penetrated to bone, which necessitated a rather grievous amputation. This, fortunately, is practically unheard of to-day.—I am, etc.,

Lunenburg, Nova Scotia. H. A. CREIGHTON.

Chloroquine in Rheumatoid Arthritis

SIR,—In "To-day's Drugs" in the *Journal* of November 8 (p. 1160) there is a note on chloroquine phosphate and its use in the treatment of rheumatoid arthritis and other diseases. A word of caution is added because of the risk of corneal deposits when using large doses. From the inquiries I have made I understand that this risk is very small, and I am hoping that this possibility will not have an adverse effect on research and the subsequent use of this valuable drug.

In my experience as a general practitioner I have had greater success in early cases of rheumatoid arthritis using chloroquine than with any other form of treatment. Two of my patients have been taking chloroquine sulphate for a year and have become almost free of pain, stiffness, and joint swelling, and in both cases the E.S.R. has fallen dramatically. I had previously watched a gradual deterioration in each one in spite of treatment with sodium aurothiomalate, phenylbutazone, and salicylates. The only evidence I have had so far of any toxicity has been nausea, with occasional diarrhoea. In cases where this occurs I now use hydroxychloroquine, and have found it to be well tolerated.

In dealing with a tragic and disheartening disease like rheumatoid arthritis, any remedy suggesting a possibility of relief is a ray of hope. Reports so far seem to suggest that this drug is safer than corticosteroids, less toxic than phenylbutazone and gold salts, and it is relatively cheap.—I am, etc.,

Kettering. W. L. OGLE.

Drug Treatment of Parkinsonism

SIR,—Dr. Macdonald Critchley in his excellent article on the use of drugs for Parkinsonism (*Journal*, November 15, p. 1214) refers to those of the solanaceous group—i.e., atropine, hyoscine, and stramonium. He reminds us that these drugs may well be used when the more recent drugs are found unsuitable.

The visual disabilities which the former may cause can be largely overcome.[1] Often 10 times the pharmacopoeial dose of stramonium is given, resulting in very marked improvement in the Parkinsonian rigidity.[2] Many of the patients, however, complain greatly of their inability to read, and of being worried by bright lights, due to paresis of accommodation and dilatation of the pupils. Roughly speaking, the stramonium effect as regards accommodation for reading distance is counteracted by a +1.50 to 1.75 lens, and eserine and pilocarpine applied to the conjunctival sac seem to counteract the effect to the extent of 1¼ dioptres. Thus those with normal refraction, who do not want to read much, can have their visual disabilities removed by miotics. Presbyopes and hypermetropes need glasses, the latter for constant wear. In children, or myopes, the use of miotics to prevent dazzle is found the best procedure. The problem is a definite one, as sometimes Parkinsonian patients have to continue with stramonium for the rest of their lives.—I am, etc.,

London, W.1. THEODORE H. WHITTINGTON.

REFERENCES

1 Whittington, T. H., *Brit. med. J.*, 1931, 2, 981.
2 Worster-Drought, C., and Hill, T. R., *Lancet*, 1930, 1, 1225.

Insomnia

SIR,—Dr. A. H. Douthwaite's article on insomnia in the series "Drug Treatment of Disease" (*Journal*, November 29, p. 1347) is most helpful. Like many brainworkers who write and study too late, I have, during 40 years, endured many bouts of sleepless nights. For these I tried many drugs as well as methods of relaxation. Of all drugs chloral hydrate was the best. It acted rapidly and left no hangover as did the various barbiturates which were formerly prescribed to be taken every night. In my dermatological practice I met many patients who complained bitterly about the depression following these drugs.

During the 1914–18 war I was in France, and found how far in advance of us the Paris physicians were in ability to treat with electricity. I learned how to apply galvanism through the brain, and to this day I resort to that when the brain is worn and weary; sound sleep is certain to come that night. I have administered it to sleepless patients for many years with success. To-day, owing to the ease of applying diathermy in hospital clinics, the modern physiotherapist does not learn how to give galvanism from a portable battery. Like many other old and tried remedies, it has unfortunately gone out of fashion.—I am, etc.,

London, W.1. AGNES SAVILL.

Physically Handicapped Children

SIR,—In the survey of pupils in schools for physically handicapped in London by Mr. W. T. Palmer and Dr. Denis Pirrie (*Journal*, November 29, p. 1326) there lies buried a fact which tends to be overlooked. Among the 1,325 children whose conditions are analysed there appear to be only 37 cases of spina bifida, and 24 cases of progressive muscular dystrophy. Those of us who are associated with residential schools for the physically handicapped supported by independent organizations are only too well aware of the fact that these two most handicapped groups have largely passed into the care of the voluntary societies, as indeed the survey points out. It is appropriate to call attention to the fundamentally greater difficulties facing those in charge of the residential schools. Running costs must necessarily be very much greater, and staffing arrangements need to be more closely related to those of hospitals.

I wonder whether the picture for London could be completed by the publication of figures showing the incidence of those "too severely handicapped for the special schools of the London County Council"? Presumably the existence and location of these children are known to the council, and it would give some indication of the trend of disability.—I am, etc.,

London, S.E.19. D. F. ELLISON NASH.

Haemolytic Disease of the Newborn

SIR,—In the article by Dr. G. A. Kelsall and Mr. G. H. Vos and Mr. R. L. Kirk, entitled "Case for Induction of Labour in Treatment of Haemolytic Disease of the Newborn" (*Journal*, August 23, p. 468), certain conclusions are reached which do not seem justified by the evidence presented.

It would appear that the authors have been able to demonstrate a correlation between the titre of the maternal Rh antibodies, as determined by the indirect anti-globulin test, and the severity of the disease in the infant when born (see their Table I). It is, however, difficult to reconcile this apparent relationship with the fact that, using this method to prognosticate in 43 Rh-negative infants, 17 were thought to have a one-in-four chance of not surviving and five a three-in-five chance of dying. Moreover, "most of" these Rh-negative cases were induced, with one death occurring; it is difficult not to attribute this death to the method of treatment, and it should be included in the overall mortality rate.

The foetal loss rate occurring in those cases which the authors were able to treat as they wished is surely of fundamental importance, but it is not possible to arrive at this figure from the data presented. The series is divided into two groups which are obviously not comparable; the "spontaneous" group is loaded with the great majority of the stillbirths, most of which, as the authors state, could not have been saved by their method of treatment (or indeed by any form of treatment). This "spontaneous" group also contains those less severe cases allowed to proceed to term. The induced group appears to consist of cases of intermediate severity. The overall foetal loss rate in the series (excluding the death of the Rh-negative infant) was 99 in 373 cases—i.e., approximately 26%. Thus, although a considerable number of cases in the series were treated by the authors' method ($179+x$, where x=the number allowed by design to proceed to term), the overall foetal loss rate does not differ significantly from that of the spontaneous series of Mollison.[1] This figure of the overall foetal loss appears to be the only one on which data is available in the article for comparison with other series.

If an attempt is made to construct the group treated by the author's method by adding to the induced group both the more severe cases (the stillbirths, which are called spontaneous) and the less severe cases—i.e., those with a titre of 1/128 or lower (spontaneous group, their Table IV) then the following figures are obtained:

Group	Stillbirths	Died	Survived	Total
Induced ..	4	19	156	179
Stillborn ..	48	—	13*	61
Spontaneous ..	2	1	62	65
Totals ..	54	20	231	305

* The number the authors thought might have been saved by their method.

This gives a foetal loss rate of 24% (not including the Rh-negative death), which is not better than the spontaneous series of Mollison. This artificially constructed foetal loss rate may not be correct, but is the nearest we can deduce from the available data. It seems difficult to find in the article, therefore, evidence supporting the view that artificial induction of labour and resultant premature delivery has favourably affected the foetal loss rate. Moreover, maternal complications of this method of treatment are not mentioned.—I am, etc.,

Royal Newcastle Hospital, Newcastle, New South Wales. WILLIAM F. HUNTER.

REFERENCE

1 Armitage, P., and Mollison, P. L., *J. Obstet. Gynaec. Brit. Emp.*, 1953, **60**, 605.

Excision of Atrial Myxoma

SIR,—Mr. J. R. Belcher (*Journal*, September 20, p. 742) says that a myxoma may be so friable that pieces may break off during its removal if pushed up from below. I tried in the article by Dr. F. R. Reid and myself (*Journal*, August 30, p. 531) to make it clear that this could not happen because the whole manipulation was so gentle. May I emphasize that the tumour during its removal is subjected to no more stress than before the operation? Its separation from the intra-atrial wall exerts no pressure on the tumour: the upper finger-nail cuts the pedicle across very much like peeling the skin of a banana, because the pedicle is composed only of endocardium and a thin layer of fibrous tissue. (A thick hard pedicle might cause difficulty in peeling off the tumour from the atrial wall: but such a tumour would not break up.) The myxoma then passes up into the auricle against the blood flow, but is held in the auricular incision mainly by the intra-atrial pressure and is only steadied by the lower finger. Its exit from the auricle occurs only when the auricular muscle is opened enough for it to slide out, most of the pressure coming from the blood itself, which, if anything, tends to blow fragments outwards.

In my own case, though the removal was relatively roughly performed, there was no evidence then or later of fragmentation.—I am, etc.,

Johannesburg, South Africa. L. FATTI.

Aspirin and Gastro-intestinal Haemorrhage

SIR,—Dr. L. Th. F. L. Stubbé, in his article on alimentary bleeding following aspirin therapy (*Journal*, November 1, p. 1062), seems to contradict himself in some of his statements. Using every means available to minimize the irritant effect of aspirin tablets on the gastric mucosa—giving them diluted with milk or water after meals, insisting that they be chewed or allowed to disintegrate in the mouth before swallowing, yet excluding in his main group any patient who suffered from dyspepsia—he still showed that approximately 70% had alimentary bleeding as judged by faecal occult blood tests applied with the most stringent precautions. Moreover, in 20 healthy volunteers one woman previously completely free of dyspepsia developed a gastric ulcer with severe indigestion within three weeks of taking 3 g. of aspirin per day, the symptoms abating completely within a few days of stopping it. Finally, he assessed the average blood loss in these patients who had aspirin bleeding (*70% of those who took them*) to be in the region of 120 ml. per month and possibly more—a greater loss than that occurring during normal menstruation.

In spite of this, he says that gastric haemorrhage and other complications "despite the frequent use of this drug have been rare," and "It is known that bleeding may occur in the stomach after a person has taken aspirin. But, considering the enormous quantities of this drug which are consumed and the frequency with which it is taken, such an occurrence may be regarded as an exception." We find it difficult to reconcile his findings and his opinions. If he meant by "gastric haemorrhage" frank haematemesis or melaena, then he is possibly on firmer ground, but even this seems unlikely.

In such an excellently controlled investigation as Dr. Stubbé's, we feel that it is a pity he did not include soluble calcium aspirin and aspirin substitutes such as N-acetyl-*p*-aminophenol ("panadol"), which we have found to have little irritant effect on gastric mucosa. On the other hand, buffered aspirin containing either glycine or alkali we have found, in common with other observers, to be just as irritant as ordinary aspirin.—We are, etc.,

Law Hospital, Carluke, Lanarkshire.

A. MUIR.
I. A. COSSAR.

Malarial Chemoprophylaxis in Indigenous Populations

SIR,—The paper by Drs. L. J. Bruce-Chwatt and D. W. Horn (*Journal*, October 11, p. 869) raises several related questions of vital importance to the indigenous populations of areas like West Africa where malaria is endemic. These questions concern: (*a*) The propriety of advising anti-malarial prophylaxis for individual families in endemic areas. (*b*) The effects of chemoprophylaxis on malarial immunity. (*c*) The correct dosages and toxicity of potent antimalarials like chloroquine and mepacrine.

It has long been held by many that the institution of drug prophylaxis among indigenes of endemic areas is dangerous, because the loss of acquired tolerance to malaria which may result might ultimately encourage cerebral malaria in defaulters. This belief has been responsible for the hesitation of the medical profession in the past to advise the public in endemic areas unequivocally on the subject. Such a view assumes

(i) that once chemoprophylaxis is instituted it will have to be continued indefinitely;

(ii) that no build-up of immunity is possible where even limited drug prophylaxis is in progress, and that in fact what immunity was originally present is lost during chemoprophylaxis;

(iii) that most families in endemic areas are unlikely to follow instructions regarding prolonged chemoprophylaxis which has proved to be of such great value in expatriates.

Assumption (i) seems reasonable in the light of our *present* knowledge, but (ii) is far from proved, while (iii) it takes no notice of contemporary developments in the fields of education and health consciousness, especially in urban communities in endemic areas, and minimizes the vast power of newspapers, radio, and other methods of mass education introduced into most of these areas in the past decade.

People who live in endemic areas know that there is no such thing as absolute immunity to malaria, because they suffer from overt attacks of malaria throughout their lives. The value of the immunity lies in preventing fatal complications of malaria, particularly cerebral malaria in the "immune" populations. This immunity is dearly bought with human lives, and at the fatal illness the blood of the child is literally packed with malaria parasites. Most of these lives might have been saved if the overwhelming malarial infections which lead to fatal complications could be prevented, without necessarily aiming at complete suppression.

The crucial questions are:

Is it possible by limited chemoprophylaxis to reduce drastically the incidence of overwhelming malarial infections (with their dangerous complications) without complete suppression of malaria? Is it possible for immunity to develop while limited chemoprophylaxis is in progress?

I believe that the answer to both questions is Yes. This idea has also occurred to others. For instance, Jelliffe,[1] after stating the other side to the case, says, "alternatively, it is possible to conceive of a new drug or one in current use but with a modified dosage which could act as a semi-suppressive preventing serious ill-effects, but permitting the development of immunity."

Here it is necessary to recall some known facts which may be relevant to the problem. First, there is the clinical phenomenon of the "break-through" when a person taking antimalarials develops an attack of malaria. This is recorded as a fact by Bruce-Chwatt and Horn and also Nicol.[2] Whatever the mechanism is, the attacks are usually relatively mild, fatal results are uncommon, and the blood often shows only *scanty* parasites. Break-throughs can usually be prevented by *complete suppression* of malaria by increasing the dose of the antimalarials, and insisting on their being taken regularly.

Another important fact is that, as recorded by Bruce-Chwatt and Horn, an increasing number of indigenes of endemic areas are taking prophylactic antimalarials. One point which they did not mention, however, is that many of us find that we need only a fraction of the recommended prophylactic dosage of antimalarials to keep away clinical attacks of malaria—e.g., 2 to 3 tablets of proguanil per week. If this limited chemoprophylaxis interfered with the level of immunity, we should have found that we need increasing doses of antimalarials over the years to keep away clinical malaria, which is not so. The inference is that this limited chemoprophylaxis is effective in preventing only severe attacks of clinical malaria, but, presumably, not subclinical parasitaemia, which helps to keep up the level of immunity.

Now there is evidence that babies born in endemic areas inherit some degree of immunity from their mothers. Their spleens are 50% heavier than those of expatriate babies.[3] I believe that they too can be protected from overwhelming and fatal malaria by limited chemoprophylaxis (e.g., 1½ tablets of proguanil a week) without complete suppression. Such a dose might still permit some build-up of immunity while preventing overwhelming infection.

A possible objection to this form of prophylaxis would be that such doses might encourage resistant strains of malaria parasites. The answer to this is that in spite of the widespread and haphazard use of antimalarials resistance has not become a clinical problem in West Africa, and has shown no signs of increasing. This contrasts sharply with the ready development of resistance to penicillin, sulphonamides, and other widely used antibiotics by certain organisms in West Africa.

Even if further experience should show such limited prophylaxis to fall below expectation, there is still a strong case for the encouragement of routine malarial chemoprophylaxis in individual families in endemic areas in the towns and the increasing numbers in the rural areas who live near hospitals, provided that the possible drawbacks of the practice are explained to them. Much can be achieved through the midwives in maternity centres, who are in regular contact with the mothers in the towns and in many rural areas.

Malaria undermines health in West Africa from the cradle to the grave and is responsible for much ill-health, high infant mortality, prematurity, anaemia, and much lowering of resistance to other diseases. The justifiable jubilation over the health of expatriates is not paralleled in indigenous vital

statistics. Yesterday the alleged ignorance of these families made the advances in malarial prophylaxis seem like a mixed blessing. To-day, however, although much remains to be done, an ever-increasing proportion of the people are wide awake and will heed instructions given in matters pertaining to health. They should no longer be denied the proved benefits of malarial chemoprophylaxis.

Finally, I agree with Bruce-Chwatt and Horn that intramuscular mepacrine and chloroquine could be dangerous, but the danger is relatively small if attention is paid to dosages. For instance, the 100–150 mg. of mepacrine musonate given by the doctors cited by Bruce-Chwatt and Horn to children under 3 is in my opinion an overdose. They should receive 50 mg., which may be repeated in 2–3 hours if necessary. The corresponding dose of chloroquine is 30 to 50 mg. of the base, which is repeatable in 1 to 2 hours.—I am, etc.,

General Hospital, Enugo, Nigeria. C. NWOKOLO.

REFERENCES

[1] Jelliffe, D. B., *Infant Nutrition in Subtropics and Tropics* (W.H.O. Publication, 1953), 1955, p. 126. Geneva.
[2] Nicol, B. M., *Brit. med. J.*, 1953, **2**, 177.
[3] Bruce-Chwatt, L. J., in *Diseases of Children in the Subtropics and Tropics*, by H. C. Trowell and D. B. Jelliffe, 1958. London.

Hypothermic Myxoedema Coma

SIR,—The therapeutic programme of the three cases of hypothermic myxoedema coma reported by Dr. Donald W. Macdonald (*Journal*, November 8, p. 1144) included penicillin intramuscularly. Two died. I have for long been under the impression that allergic phenomena are more likely in people with low basal metabolic rates. Some 15 cases of hypothermic myxoedema coma have been reported in the last five years—that is, within the antibiotic era—and the mortality is high. Is it possible that a penicillin allergy is a cause of death in such cases, and might not an antibiotic with a less notorious allergic reputation be advisable in these instances?—I am, etc.,

Cape Town, South Africa. M. GLASS.

Australian War Experience

SIR,—I have just read with interest the review by Dr. J. C. A. Dowse of the third medical volume *The Island Campaigns*, by Allan S. Walker, dealing with the Australian Medical Services in the war of 1939–45 (*Journal*, August 16, p. 432). I say with interest, particularly, because it emphasizes a criticism of this work which I had published in the *Medical Journal of Australia*.[1] You will note that the reviewer's remarks are correctly and interestingly written in accordance with what this volume contained, and thus his opening sentence, naming only the mosquito as a more deadly enemy than the conventional weapons of war, gives a very inaccurate (through no fault of the reviewer) overall picture of the medical hazards of the campaigns in question. Further along, the reviewer rightly states, "Much is told of the work of individuals in field ambulances and sections of those units; little of the work of the casualty clearing stations or general hospitals."

In order to place the medical hazards encountered in the South-west Pacific Islands in their proper perspective, may I refer your readers to my communication to the *Medical Journal of Australia* already mentioned? There they will see that, through unfortunate and unavoidable circumstances, practically all reference to skin diseases was omitted. Here I would again refer your readers to chapter 55, page 619, in the first volume of this series, *Clinical Problems of War* (also by Allan S. Walker), where it will be seen that for a long period skin diseases were a greater cause of manpower wastage than any other condition, including malaria. I have made a number of attempts to get the over-all Australian war historian to publish a short addendum to the third volume, to correct the very erroneous impression it gives in its present form as to the relative importance of the various causes of manpower wastage, in case such wastage should ever become important at some future date. However, my efforts have, so far as I am aware, produced no constructive results.—I am, etc.,

Faculty of Medicine, University of Sydney. J. C. BELISARIO.

REFERENCES

[1] *Med. J. Aust.*, 1958, **1**, 304.
[2] Walker, A. S., *Australia in the War of 1939-1945*, Series 5, Medical, Vol. I, 1952, p. 619. London.

Foreign Body in Endotracheal Tube

SIR,—I note a letter from Dr. K. A. Stewart (*Journal*, November 15, p. 1226) describing obstruction of an endotracheal tube by a cork. I have always advocated routine inspection of the tube to be used, thereby on one occasion avoiding using a tube blocked by a piece of cotton-wool.—I am, etc.,

Newport, Monmouthshire. K. S. THOM.

SIR,—The letter in the *Journal* of November 29 (p. 1357) by Mr. E. H. Rainer is one of several reporting blocked endotracheal tubes. No further letters need be written, thus saving valuable space, if a curved metal introducer is inserted into the tube before oral intubation.—I am, etc.,

London, W.3. E. V. SLAUGHTER.

Fermented Liquors and Disulfiram

SIR,—Alcoholics on disulfiram ("antabuse") do occasionally accidently ingest alcohol with the resultant toxic symptoms. This is usually the result of misguided friends "spiking" a soft drink. The following incident is unusual, and so far as I know has not been reported in the literature.

A middle-aged and co-operative female alcoholic had been in hospital for three weeks and had been on disulfiram for six days. She had had no side-effects, but one morning complained of nausea, vomiting, flushing of the face, palpitations, and oppression in the chest. There was a distinct smell of acetaldehyde on her breath. Naturally, it was assumed that she had obtained alcohol in some form from a visitor. This was strongly and tearfully denied, and the searching of her locker failed to reveal any alcohol.

As well as the usual vitamin therapy she had expressed a wish for one of the proprietary malt preparations which she had been taking three times daily for about a week. On opening the jar of malt it was obvious that fermentation had taken place, and subsequent analysis confirmed the presence of alcohol.

This may be a hazard peculiar to hot countries, but it certainly indicates how careful patients on disulfiram must be to avoid accidental contact with alcohol.—I am, etc.,

Ndola, Northern Rhodesia. DONALD WHITFIELD.

Rational Use of Drugs

SIR,—In common with other medical practitioners I have received a copy of the very helpful booklet[1] which sets out the relative cost of proprietary preparations and their equivalents. Recently, when wishing to prescribe a suitable preparation for threadworm infestation, I referred to the booklet to see whether there was any difference in cost between "elixir antepar" and the *B.N.F.* equivalent, elixir piperazine citrate. Discovering that the latter is considerably cheaper, I duly ordered that. However, the dispenser actually issued the proprietary, as that was the only preparation in stock. As a result, my earnest endeavour to play a part in the much-needed drive for economy was frustrated. What is the answer to this? I imagine that this is by no means an isolated example.—I am, etc.,

Halifax, Yorks. MALCOLM B. BUTLER.

REFERENCE

[1] N.H.S. Pharmaceutical Services: Costs of British National Formulary and Proprietary Preparations, July, 1958.

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[1] March 1955. p.62
[2] C.R. Soc. Biol. (Paris), 1948, 142, 819

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Pharmaceutical Houses and the Doctor

SIR,—I am reluctant to contradict one of my respected teachers, but Professor S. J. Hartfall (*Journal*, December 6, p. 1411) is wrong when he says that the *British National Formulary* contains all that we require for our sick patients.

The *Formulary* is deficient in children's remedies. There is no liquid preparation of penicillin V, tetracyclines, or antihistamines, nor is there any oral streptomycin for gastroenteritis. Perhaps there are technical reasons for these omissions, but it is certainly in treating children that I use most proprietary medicines.—I am, etc.,

Bradford, 5. G. B. HILL.

SIR,—While hesitating to criticize the opinions (*Journal*, December 6, p. 1411) of a member of the Joint Formulary Committee, I would like to put forward a point of view which other general practitioners may share. The *British National Formulary* is a first-class book, and 90% of my prescribing is based on it. Its amendments, however, are clumsy, and even the most recent one does not include, for example, tab. chlorothiazide, tab. mecamylamine, or a mist. kaolin. et neomycin. pro inf. We must be much more up to date than that, not only for our own prescribing, but to keep pace with the consultant who suggests that we use a proprietary drug previously unknown to us. *Prescribers' Notes* are no help here, and most doctors exercise enough judgment to be able to do without *Proprietary Medicines*. "To-day's Drugs," while written in a suitably critical manner, is difficult to file for easy reference, and "Drug Treatment in Disease" is out of date as soon as a new drug of proved value is produced.

Most of the pharmaceutical firms are doing a good job, as Dr. S. Bradshaw (p. 1411) says, and it is mainly in the method of distributing information that some of them fail us. The solution offered by Dr. J. A. Frais (p. 1412) is a nutcracking sledge-hammer. No, the whole answer has already been provided by Dr. J. D. W. Whitney in his article "Modern Pharmaceutical Advertising" (*Supplement*, July 13, 1957, p. 7). His scheme could be operated at far less than the cost estimated by Dr. J. Phillips (p. 1413). Although about 25 firms have already taken his remarks to heart, I am sure that quicker results could be obtained if the B.M.A., the Association of British Pharmaceutical Industry, and the Ministry of Health would discuss the matter together.—I am, etc.,

Walsall. J. P. LESTER.

SIR,—May I reply to the letters on "Pharmaceutical Houses and the Doctor" in the *Journal* of December 6? I would like to inform Professor S. J. Hartfall (p. 1411) that the questionary I completed was in the form of a postcard brought into my surgery by a cheerful representative. I placed a few ticks in appropriate squares "for research purposes." As for writing *letters* to the *British Medical Journal*, the letter published on November 22 (p. 1291) was the first letter I have ever written in my life to any publishing body. I was writing merely as a general practitioner whose surgeries get more like commercial television every day. This week, on Wednesday morning, my surgery was interrupted four times by representatives who entered when I rang for the next patient. There I am—trapped—while my patients cool their heels and I champ at the bit. I know I could ease my lot by throwing all the literature unopened into the waste-paper basket and hang a "keep out reps" notice on the door—but is this really the right solution? Professor Hartfall says my patients will not suffer if I do this. Dr. S. Bradshaw (p. 1411) tells me that useful life-saving drugs will remain unrecognized for periods of time varying from 12 to 40 years. Who am I to believe?

Yes, I repeat, I *am* "a simple family doctor," with an innate sense of courtesy, not a churlish, disagreeable cynic, an analytical scientist, a combine harvester made for sifting proprietary products . . . nor yet a social butterfly, flitting from cocktail parties to dances at the expense of time spent in the surgery. (I have been to nine dances since 1945 and fewer cocktail parties, and on no occasion have I had a medical representative as an escort, charming though they may be!)

Of course, I use the *British National Formulary*. I am fortunate enough to receive every new edition gratis from the executive council. It is my best friend; I have a current copy on my desk, one in my case, one at the hospital, and another at the treatment centre. However, this does not stop the continual bombardment to which I am subject. I receive *Prescribers' Notes* too, but new drugs come out much faster than either of these.

My own experience tells me that if I prescribe certain products that are "freely prescribable on E.C.10s," according to the representatives, I would receive a letter from the executive council informing me that I shall have to pay the cost of the drugs out of my own pocket. Each locum I have engaged has unknowingly left me a legacy of such chitties and I am responsible for their payment. It is therefore with relief that I hear that final-year medical students are encouraged to write prescriptions and are to be proud possessors of a good pharmacopoeia. Whether it is *Martindale*, the *British National Formulary*, a special hospital pharmacopoeia, or a personal one compiled from one's own experience, it is invaluable and, I maintain, will contain much valuable material so neglected nowadays in the *British Pharmacopoeia*. I do not deplore the fact that G.P.s do not use the *B.P. per se*. I deplore the fact that we are being boggled by firms who change the name of the rose, wrap it in cellophane, and charge more for it.

As for Dr. Bradshaw's attack, I have already answered some points in his letter. I am not discussing my own remuneration or the price I have to pay for drugs. That is entirely irrelevant. My worry is that I am acutely aware of the fact that every single time I write a prescription I am spending *other people's* money, *not* my own. It is a heavy responsibility and I must not be too gullible or be misled by the glossy advertisements. (I object to the glossiness because it limits its domestic uses. They are more difficult to dispose of: some of them will not even burn.)

Advertisement psychologists are people who earn about four times as much as the average general practitioner, so I am told. They are used for increasing the sales of products.

Yes, I am in favour of research, but if you cannot afford to do all the vital research you desire, do not give so much away to charities or spend so much on advertising material or sending representatives so frequently to sit in our waiting-rooms. I am in agreement with exporting, but from my ever-increasing collection of foreign stamps I am wondering how many millions of pounds worth of drugs we are importing.

Finally, Dr. Bradshaw, my Utopias are dreamt up in my car in between the visits which are sometimes delayed by sorting through a heavy post or listening to the properties of a new wonder drug.

I agree with Mr. R. Merryweather Shaw (p. 1413), hospital pharmacists and local chemists are an invaluable boon to the busy doctor. They are not riding a hobby horse to increase the sales of any particular firm. They are keen on dispensing, not being shop assistants.

Dr. Geoffrey F. Baines (p. 1413) is right. It is difficult to sort out problems. I discovered that several proprietary products were cheaper than the *British National Formulary* equivalents. As a result I prescribed these preparations in an attempt to save national expenditure. When my drug bill was analysed, I was asked why I had prescribed proprietary products instead of *British National Formulary* equivalents. Professor Hartfall may be astonished to learn that I was also asked whether I always prescribed the drugs advised by hospital consultants when I have asked for a second opinion. General practitioners are working under difficult and exacting conditions; all we want is understanding, *honest* co-operation.—I am, etc.,

Birmingham, 30. MARY M. RAYNER.

*** This correspondence is now closed.—ED., *B.M.J.*

Proper Use of Words

SIR,—Recently, in a Very Important weekly medical journal, a Very Important Cardiologist stated that a patient collapsed "following a large haemoptysis."

I remember a colonel who collapsed following a large tiger and a South American band-leader (obese and no

longer young) who collapsed following a large blonde. But why, I asked myself, should anyone follow a large haemoptysis? My first thought was that he was a "time-expired registrar" who intended to write a paper about haemoptysis: my second that "haemoptysis" was a misprint for "hippopotamus." Dr. H. M. Sinclair's letter (*Journal*, November 29, p. 1559) provides an alternative explanation. Could the Very Important Cardiologist have meant that his patient collapsed *after* a large haemoptysis? What a dull solution of a fascinating problem!—I am, etc.,

London, S.W.3. RAYMOND GREENE.

SIR,—My old friend, Dr. Hugh Sinclair, very properly criticizes my style (*Journal*, November 29, p. 1559). However, not everyone would agree with him. My friend Lord Cohen has pointed out that Fowler[1] says:

"*Firstly, secondly, lastly.* The preference for *first* over *firstly* in formal enumerations is one of the harmless pedantries in which those who like oddities because they are odd are free to indulge, provided that they abstain from censuring those who do not share the liking. It is true that *firstly* is not in Johnson; it is true that De Quincey labels it 'your ridiculous and most pedantic neologism of *firstly*'; the boot is on the other leg now; it is the pedant that begins his list with *first*; no-one does so by the light of nature; it is an artificialism. Idioms grow old like other things, and the idiom-book of a century hence will probably not even mention *first, secondly*."

Dr. Sinclair ends his letter with an admonition in Greek which I fear few of your readers will understand, which is a pity, because the function of language is to convey meaning. "Physician heal thyself" is not easily achieved. A writer cannot remedy his own defects of style unless he himself recognizes them, or they are pointed out by others. Nowadays it is difficult to find the time to read meticulously what one has written. It is no criticism of you, Sir, to say that the Editor who unfailingly notes the kinds of faults which Dr. Sinclair notes is now, from similar causes, almost extinct. Good writing is not something whose decay one watches with equanimity. I bow my head to Dr. Sinclair's strictures. Would that the physician could heal himself.—I am, etc.,

University of Oxford. G. W. PICKERING.

REFERENCE

[1] Fowler, H. W., *A Dictionary of Modern English Usage*, 1926. Oxford.

SIR,—In your issue of November 29 (p. 1359) Dr. H. M. Sinclair takes the Oxford regius professor of medicine to task for the misuse of words and lack of clarity in a recent address (*Journal*, November 8, p. 1117). The letter ends with this observation, "In the singular opinion of a former student of Sir George's who admires his addresses, we should all avoid unnecessary jargon and the improper use of words." Does this sentence mean that Sir George admires Dr. Sinclair's addresses or vice versa?—I am, etc.,

West Malvern. W. G. SHAKESPEARE.

Women Police Surgeons

SIR,—Dr. Nesta H. Wells's account of her 27 years' service as a Manchester City police surgeon (*Journal*, December 6, p. 1404) is both interesting and informative. But I do not follow her reasons for supposing that women doctors (*per se*) are better suited for dealing with children. I have heard similar postulations applied in other branches of medicine—for example, in gynaecology—and I think the idea is both retrograde and old-fashioned. Surely the sex of a doctor is not so important as the innate qualities of kindness, patience, and understanding. Does Dr. Wells feel that male doctors are lacking in these?

Regarding the cases she describes, I submit that our chief concern should be in their prevention (rather than after-treatment or punishment), and that this starts in the home—for adults, as well as children.—I am, etc.,

Knowle, Warwickshire. N. W. SARGENT.

Obituary

ERNEST SACHS, M.D., F.A.C.S.

Dr. Ernest Sachs, the eminent American neurosurgeon, died in hospital at New Haven, Conn., on December 2. He was in his eightieth year and had been ill for only a short time.

Having been professor of clinical neurological surgery at Washington University, St. Louis, from 1919 to 1946, Ernest Sachs went to Yale at the age of 70 as research fellow in physiology, and it was at New Haven he completed his *History and Development of Neurological Surgery*. Well known as a neurosurgeon, teacher, and writer on both sides of the Atlantic, he had many friends in Britain, for which, as one who had sat at the feet of Sir Victor Horsley, he had a particular affection. When the centenary of Sir Victor Horsley's birth was celebrated last year, Dr. Sachs contributed to this *Journal* some "Reminiscences of an American Student" (April 20, 1957, p. 916), paying this tribute to his mentor: "As I look back upon the years I spent with Victor Horsley, I feel he gave me the best possible insight into the life of a broadminded, generous scientist of his generation." Dr. Sachs's own students felt much the same about him.

Sir GEOFFREY JEFFERSON, F.R.S., writes: The death of Dr. Ernest Sachs means to many engaged in neurosurgery and neurology the passing of a warm and loyal friend. He has told the story of his life in a recent book, *Fifty Years of Neurosurgery—A Personal Story* (1958), and an important document it is, because it covers the whole period of the rise and development of the surgery of the nervous system from Horsley's day onward. Born in New York, the nephew of the famous neurologist Bernard Sachs, he graduated from Harvard and from the Johns Hopkins Medical School, where he was a pupil of Halsted and Osler and came to know Cushing. Ernest Sachs worked with Sir Victor Horsley for a twelvemonth 1907–08 at Queen Square and in his laboratory at University College on the structure and function of the optic thalamus. Sachs became the friend of the Horsley family and a permanent and devoted admirer of Sir Victor, of whom he has written generously.

Sachs will be remembered as a pioneer because, declining an offer to join Cushing, he accepted an invitation in 1911 to go out to the mid-West, to the newly founded Washington University in St. Louis, Mo. This was a courageous move, for at that date there was little specialized neurosurgery anywhere except in Baltimore, Philadelphia, and New York. When he was young there were scarcely a dozen neurological surgeons in the world; now there are over a thousand in the U.S.A. alone. Sachs's tremendous energy, his frank and attractively dynamic personality and complete scientific integrity ensured the success that came his way in plenty. It is impossible in a few words to convey a proper impression of the bubbling warmth of his abundant personality. He was a member of all and had been president of most of the important neurosurgical societies of America and of the American Neurological Association. He was a valued honorary member of our own British Neurological Society and of the Neurological Section of the Royal Society of Medicine.

After his retirement he moved to New Haven, where he helped with the teaching of Yale undergraduates. Sachs wrote several books which had a wide public: one arising from his famous clinical demonstrations to the students at St. Louis is very wise. All those who knew Ernest Sachs well—and if one knew him at all one was sure quickly to want to know him better—will feel sorrow now and sympathy with his charming wife, Maisie, his constant companion.

J. M. C. SPEER, M.D., D.P.M.

Dr. J. M. C. Speer, formerly medical superintendent of Roundway Hospital, Devizes, died in Dublin on October 20. He was 56 years of age.

James Millar Craig Speer was born in Co. Donegal on November 17, 1901. He proceeded from Foyle College, Londonderry, to the Queen's University, Belfast, where he graduated M.B., B.Ch. in 1924. In 1925 he was appointed an assistant medical officer at the Wilts County Mental Hospital, as it then was, and devoted himself to psychological medicine, taking his D.P.M. in 1928. He became deputy medical superintendent in 1934, and in the following year proceeded to the M.D. with a thesis on dysentery in mental hospitals. In 1947 he succeeded the late Dr. J. F. W. Leech as medical superintendent of Roundway Hospital. Four years earlier he was appointed to the commission of the peace for the borough of Devizes, and on the bench his special knowledge was highly valued. He was chairman of the Trowbridge Division of the British Medical Association in 1948–9.

J. O. D. writes: Millar Speer brought high professional abilities and personal qualities to all his life and work. He kept abreast of advances in psychological medicine and introduced new methods of treatment of mental illness. He undertook with quiet efficiency the heavy increase in both administrative and therapeutical work occasioned by the inauguration of the National Health Service. To all his work he brought knowledge and diligence, good judgment and imagination. Above all else he was a doctor, happier in a ward than in an office. He retired to Blackrock, Dublin, with his wife in 1957, to enjoy only eighteen months of quieter life. At Roundway Hospital his memory is cherished for the personal qualities that marked his relationship with staff and patients. Speer was a man of flawless integrity and an imperturbable temper. Essentially humble-minded, he was infinitely patient and gentle in manner. With his imaginative understanding and quiet humour he won the confidence and regard of everyone. In Millar Speer the injunction was abundantly fulfilled—"He that is chief among you, let him be as he that serves."

A. D. WALL, M.B., F.R.C.S.

Mr. A. D. Wall, senior surgeon at the Paignton and District Hospital, died at Paignton on November 25, aged 62.

Austin Darley Wall was born on August 1, 1896. From Oundle he went on to St. Bartholomew's Hospital, where he was awarded the junior and senior scholarships in anatomy and physiology, and won both the Harvey and Foster prizes. Qualifying in 1918, he graduated M.B., B.S. in the following year. After serving in the Royal Navy for a time he held a number of resident appointments at Bart's, and, deciding to specialize in surgery, he took the F.R.C.S. in 1921. A few years later he went out to Shanghai, where he became honorary surgeon to the Shanghai General Hospital and to the Lester Chinese Hospital. He was also medical officer to the British Consulate and to the Shanghai Municipal Police. Returning to Britain shortly after the outbreak of the second world war, he came to live in Paignton. Early in 1940 he joined the R.A.M.C. and served as a surgical specialist until 1945, being mentioned in dispatches. On demobilization he returned to Paignton, where he was in general and surgical practice until his death. He was elected President of the Torquay and District Medical Society this year. He leaves a widow and two daughters.

J. F. B. writes: Mr. Wall as a person was extremely kind, patient, and courageous. No one ever saw him flustered, nor heard his voice raised in anger, yet he was energetic and determined in all his activities. As a consultant surgeon he was always practical and helpful, perhaps because he was also a general practitioner himself and understood the nature of a family doctor's problems, and he was not above doing the most lowly surgical chores—a necessary asset when running the surgical services of a general-practitioner hospital with no resident staff. To this last quality can be attributed the opinion of a patient who said that he liked Paignton Hospital and thought the staff very kind and efficient, particularly the house-surgeon—the house-surgeon in question being Mr. Wall. His modesty was outstanding, and he was endowed with a sense of humour which always seemed to manifest itself unexpectedly, but kept on appearing regularly. His devoted work at Paignton, and the high quality of that work, will be much missed; but mostly we mourn the loss of a much-loved man.

Medico-Legal

MOTHER'S ADOPTION OF ILLEGITIMATE CHILD

[FROM OUR LEGAL CORRESPONDENT]

On November 28 the Court of Appeal decided (*The Times*, November 29) for the second time that there was no good reason in principle why an order should not be made under the Adoption Act, 1950, by which an unmarried mother could adopt her own child. The court's previous decision had not been reported, because it was given *in camera*.

The matter arose on appeal from a refusal by a county court judge to make the order on the application of the mother and on a report by the L.C.C. Welfare Officer that the child was well cared for and adoption seemed to be in her best interest. The judge had taken the view that the Adoption Act, 1950, had not been designed or intended to remove the stigma of illegitimacy, and that if he made an order it would be a precedent which would soon become common form and result in the abolition of illegitimacy.

In his judgment Lord Denning said that it was plain from the terms of Section 1 (3), Section 2 (1), and Section 12 (2) of the Act that Parliament had contemplated the making of an order in such circumstances. There were many advantages for the child if an order were made, in the field of the inheritance of property for example and by using the registration in the adopted children's register instead of the entry in the register of births. The child remained illegitimate even if adopted, but by being adopted it became in law the child of its mother for all purposes and so suffered none of the legal disabilities which attached to illegitimacy. If the mother was a suitable person and the home and other circumstances were suitable, the fact that the order was sought simply because the child was illegitimate was no bar to it being made.

Lord Justice Hodson added that the exercise of the court's discretion was of course required to see whether the mother could look after the welfare of the child, since the welfare of the child was the paramount object of the Act.

MAINTENANCE WHERE SPOUSES PART FOR MEDICAL REASONS

[FROM OUR LEGAL CORRESPONDENT]

Recently the Divorce Divisional Court upheld the refusal of the Kingston-upon-Hull magistrate to make a maintenance order against a husband whose wife was living apart from him for medical reasons (*The Times*, October 30).

The parties were married in 1948 and things went reasonably smoothly till 1952, when after a very difficult confinement the wife became a voluntary patient in a mental hospital. There she stayed until 1956, when she went to live with her mother because she suffered from a neurosis which produced acute revulsion to sexual relations, and if she had returned to live with her husband she would have had a serious breakdown in health.

In his judgment the President said that on the facts the husband was not in desertion, nor had he agreed to maintain her as a separated wife, so that wilful neglect to provide reasonable maintenance for her could not be imputed to him. The true solution to this difficult case was for the National Assistance Board to ask for an order for the wife's maintenance under Section 43 of the National Assistance Act, 1948, which could be made without any "wilful neglect" on the husband's part being established.

Medical Notes in Parliament

MENTAL ILLNESS

Research Projects

Dr. DONALD JOHNSON (Carlisle, Con.) asked the Minister of Health on December 8 whether he was satisfied with the adequacy of the machinery for approval of mental health research; in particular, whether this was acting quickly enough; and if he would make a statement. Mr. D. WALKER-SMITH: Yes. The machinery provides for rapid and regular consideration by the Medical Research Council of proposals and of the advice tendered by the Clinical Research Board about them.

Dr. JOHNSON said that in spite of what the Minister said complaints were received that it took sometimes 18 months to obtain a definite answer, Yes or No, on a research project, and delays of that kind were frustrating. Mr. WALKER-SMITH said he knew of two cases in which there had been unavoidable delay for personal reasons connected with the gentlemen who were to be put in charge of the projects. In the ordinary way the machinery was designed to be rapid, and was so in practice.

Mr. A. BLENKINSOP (Newcastle upon Tyne, East, Lab.) said that recently a number of scientists and medical men doing mental research, especially on schizophrenia, had been lost to the United States, and there was some anxiety about this trend. Mr. WALKER-SMITH explained that in one of the cases the professor concerned had taken an appointment in the United States. That was the reason for the delay. But the action was taken for personal reasons, and general conclusions of the kind Mr. Blenkinsop had mentioned should not be drawn from it.

Local Authority Welfare Services

Mr. BLENKINSOP asked what additional local authority expenditure on mental health and welfare services has been approved for 1959–60 and 1960–1. Mr. R. THOMPSON, Parliamentary Secretary, Ministry of Health, said that included in the figures of relevant expenditure taken into consideration in fixing the proposed totals of general grant for the first grant period were estimated amounts for these services of over £900,000 for 1959–60 and over £1¼m. for 1960–1 above the estimated figures for 1958–9.

Mr. BLENKINSOP asked if he thought these figures would make possible any kind of start in developing local authority services to provide for the numbers who would be able to come out of mental hospitals and institutes. Mr. THOMPSON: Indeed I do. It is estimated that the rate of development for which these increases provide in each year is about two and a half times the annual development rate achieved in recent years. Mr. BLENKINSOP: The Parliamentary Secretary knows that during the last few years there has been hardly any development at all. Why try to confuse the House by talking about two and a half times a rate of increase that has been negligible? Mr. THOMPSON said he could not accept that what was now spent on these services was negligible. A rate of two and a half times greater was considerable by any standards.

Consequences of Rutty Case

Mr. N. DODDS (Erith and Crayford, Lab.) asked the Minister in view of the decision in the High Court on the illegal detention of Miss Kathleen Rutty, which resulted in her discharge as a mental defective, and the subsequent review of those mental defective patients detained under the same section of the Mental Deficiency Act, 1913, how many patients had been discharged as a result of this review; how many were still detained under this particular section of the Act; and why they had not yet been released. Mr. WALKER-SMITH: 1,957 have so far been discharged; 3,078 are still detained because they are unfit for discharge or have nowhere suitable to go.

Mr. DODDS expressed his delight that nearly 2,000 people who had been wrongfully certified had now been allowed out. But was it not a terrible indictment of the country that 3,000 people should be detained who had never been certified, largely because there was no other place for them than mental institutions? He asked the Minister to undo some of the wrong which had been done. Was it possible to give them some special rehabilitation courses to smooth their way back into the community? Mr. WALKER-SMITH pointed out that they did not know that all these cases were similar to the Rutty case, because they did not know the facts that were before the court. The board was not in a position at any time to know the facts before the court at the time of admission. These were cases which appeared on the face of it to have some similarity, but he was sure that what Mr. Dodds had in mind was that the basis of the Rutty decision was on the construction of the words "found neglected." There was no doubt that many of these 3,000 people were in need of care and treatment for their mental condition. Mr. DODDS: Yes, but not in mental institutions.

Sir GODFREY NICHOLSON (Farnham, Con.) said the anxiety and shame expressed by Mr. Dodds were widely shared on the Conservative side. Mr. WALKER-SMITH replied that before he used those expressions he should study the facts and realize what was the basis of the Rutty decision.

Leucotomy Operations

Mr. K. ROBINSON (St. Pancras, North, Lab.) asked how many leucotomy operations had been performed in mental and mental-deficiency hospitals in England and Wales during each of the last 10 years. Mr. WALKER-SMITH said the only information available was as follows: The numbers of leucotomy operations performed in N.H.S. hospitals in England and Wales in each of the years 1949 to 1952 were, respectively, 1,442, 1,337, 1,308, and 1,355. A special inquiry showed that, in 1957, 728 operations were performed in regional hospitals with 100 or more beds.

"Persomnia"

Mr. F. NOEL-BAKER (Swindon, Lab.) asked what steps the Minister would take to place the tranquillizing drug "persomnia" on Schedule 4, in view of the widespread anxiety in the medical profession about its unrestricted sale to the public and the danger of addiction. Mr. WALKER-SMITH said the Home Secretary had informed him that the Poisons Board was not prepared to recommend this. At the Board's suggestion, the problem was being referred to the Interdepartmental Committee on Drug Addiction.

CONDUCT OF MEDICAL RESEARCH

Experiment on Children

Mr. S. SWINGLER (Newcastle-under-Lyme, Lab.) asked if the Minister had considered the report sent to him of a clinical experiment in which mentally defective children in hospital were used as matched controls; whether parental consent was obtained before the children were so used; and what assurances were given that no harmful effects would result.

Mr. WALKER-SMITH: I have seen the report, and I regret to find on inquiry that parental consent was not obtained as it should have been before the drug was administered. I am assured that a single dose as given in this case has no harmful effects.

Mr. SWINGLER recalled that in February, 1945, he had called attention to a similar case of children in hospital

THE PROBLEM

To obtain high blood levels of theophylline easily . . .

For oral aminophylline therapy to be fully effective it is necessary to give a dose sufficient to produce high blood theophylline levels. However, because of gastric irritation vomiting often results. Alternative therapy with enteric coated tablets or suppositories is unreliable, and parenteral aminophylline is inconvenient.

THE SOLUTION

Oral 'Theodrox' . . .

The combination of dried aluminium hydroxide gel and aminophylline in 'Theodrox' ensures full therapeutic response with the minimum of gastric upset. Reproduceable blood levels comparable with those obtained from intramuscular injection can be obtained.

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Recent work[1,2] has shown that synthetic derivatives of theophylline are mostly unsatisfactory and all are more expensive.

Each 'Theodrox' tablet contains 3 grains aminophylline and 4 grains dried aluminium hydroxide gel. 'Theodrox' is also available combined with $\frac{1}{8}$ grain phenobarbitone where a degree of sedation is also required.

REFERENCES

[1] *Brit. med. J.* (1957) *2*: 67

[2] *Ibid.*, page 74

DOSAGE . . .

ASTHMA:— two tablets, repeated in 2-3 hours if necessary to control paroxysm and dyspnœa. For prophylaxis, one tablet 4 times daily.

DIURETIC:— two tablets initially, then one or two tablets three times daily.

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PACKS:— Bottles of 25, 100 and 1,000 tablets.

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VITAMINS LIMITED ANNUAL GENERAL REPORT

"Pharmaceutical Industry responsible for only 1/10½d in the £ of increased N.H.S. costs"

AT THE Annual General Meeting of Vitamins Ltd., held recently in London, Mr. H. C. H. Graves, Chairman, said that net profit for the year, after providing for pension and tax allocations, was up from £90,409 to £146,161. Ordinary dividend was increased from 17½% to 20%.

Mr. Graves said in 1955 he had stated that the Company had shots in the locker with fuses timed to go off in 1957, 1958 and even later. This was still true.

The most important project they had in hand appeared, at the moment, to be assured of a market and the question was the production of "pay" quantities quickly. If this could be done the project could be largely self-financing, but they were often hampered by what seemed to be inordinate time lags in the delivery of machinery.

Competition in their established lines continued severe and while they had the technical resources to meet and to excel all competition on grounds of quality and, he hoped, of price, it would require the most determined efforts of their hard-working and devoted staff, to maintain and improve the striking position gained over the past few years. They hoped to do it and to make further progress.

A month or so ago said Mr. Graves, the Ministry of Health's Annual Report for 1957 had shown an increase of £50 million in N.H.S. costs in one year, or £301 million increase since 1948. What were these increases mainly due to? It was safe to say that if this question were asked as a general knowledge test 99 per cent. of the general public and many leaders of opinion would give the wrong answer.

The correct answer was that £202 millions were due to increases in hospital costs (for salaries, fuel, provisions, bedding, etc.). Only £28 million of the nine-year increase went to drug manufacturers for drugs which—among other things—had saved the lives of several millions of people in this country alone since the N.H.S. started.

To put the matter in another way, of every £ of increased costs, the drug manufacturer had had 1/10½d. In their eagerness to assail him for the 1/10½d. (for which he had given amazing value in life-saving drugs as in many other ways) the critics forgot the other 18/1½d.

The role of the Company's product, Bemax, as the best-known vitamin-mineral-protein food in the world, continued to be appreciated and understood by doctors and dietitians, by nurses and mothers as it had been for the past thirty years. If, like some regimes, Bemax were unpleasant and not easy of acceptance, he could understand there being abstainers from its use. On the contrary, Bemax with milk or fruit juice, in soup or sprinkled on cereal foods was so delicious and added such zest to life that he really found it incredible that anyone who had the opportunity should fail to give it a trial, and still more incredible to think anyone, these days, could be found to deny their children its benefits and the protection which it afforded. The report and accounts were adopted.

VITAMINS FROM VITAMINS LIMITED

UPPER MALL, LONDON, W.6

being used as "guinea-pigs" for scientific experiments involving the injection of drugs without there being any parental consent. Was this not very wrong, and as a second case had occurred should not the Minister issue some guidance to hospital authorities? There were many people who had the strongest objections to children being used in this way, especially when adults could volunteer for the purpose. Mr. WALKER-SMITH replied that guidance had been issued in the form of the Medical Research Council memorandum, which had been published. With regard to adults, in this case the drug was first tried out on the doctors who were to carry out the trials on the children.

Regulation of Clinical Experiments

Mr. SWINGLER asked to what extent the regulations permit the use of children in hospital for clinical experiments with or without parental consent. Mr. WALKER-SMITH: Investigations of this kind involve medical and ethical problems which are not susceptible of control by regulations. It is, however, my view that parental consent should be obtained, and I will draw the attention of responsible officers of hospital boards to this matter again.

Mr. SWINGLER said it was regrettable that this case should have occurred. "Will the Minister now make this instruction very emphatic to hospital authorities, so that no further cases may occur?" he asked. Mr. WALKER-SMITH: I will certainly try to ensure that the requirement is brought to the notice of all concerned. Having said that, I reiterate that no harm was done and that this was a valuable and useful experiment.

Mr. C. MAYHEW (Woolwich, East, Lab.): While the Minister rightly agrees to look carefully at the point raised by Mr. Swingler, will he bear in mind that a number of very promising research projects involve free access to patients? While he will look carefully at the matter, may I ask that he will not prejudice the success of those important researches? Mr. WALKER-SMITH: My general policy, in harmony with that of the Medical Research Council, is that there should be the greatest possible freedom from detailed supervision of clinical research in hospitals, for the reasons Mr. Mayhew has given. I do not regard that as incompatible with abiding by the view I have expressed about parental consent for these cases.

Expenditure on Cancer Research

Mr. H. HYND (Accrington, Lab.) asked the Minister what new steps he was taking to tackle the disease of cancer; how much he had spent from public funds on research into this disease during the last 12 months; and what amount had been contributed from other sources for this research in institutions for which he is responsible. Mr. H. ATKINS (Merton and Morden, Con.) asked what was the total of public funds to be spent on cancer research in this financial year, including both the block grant to the Institute of Cancer Research and any part of the general grant-in-aid to the Medical Research Council which was used for this purpose.

Mr. WALKER-SMITH: In the current financial year the Council's estimated expenditure on cancer research from public funds is £472,470; in addition, it is estimated that some £26,500 from other sources will be expended by the Council, approximately half of which will be in the Council's own research units and groups. In addition to the Council's expenditure in this field, further research is supported from public funds in the N.H.S. in the course of the treatment of patients; and in various university and medical school departments from University Grants Committee funds. It is, however, not possible to make a separate estimate of this expenditure. Every effort is constantly being made to achieve a break-through in this very difficult field, and the Medical Research Council will continue to develop its programme and to follow up every promising new approach.

Mr. HYND said he appreciated what was being done, but was the Minister happy about the appeals that had to be made for private charitable contributions to such an important project? Mr. WALKER-SMITH: I see nothing improper or unacceptable about private organizations and private funds supplementing the public effort. Cancer research is the sort of thing that ought to attract private as well as public support, and there is close co-ordination regarding the common objects of research.

Mr. ATKINS said that this expenditure was an investment in the future and would pay extremely good dividends. Would the Minister so represent it when he asked the Chancellor of the Exchequer for an increased grant next year? Mr. WALKER-SMITH: The amount of money available is such that cancer research is not handicapped by lack of funds. It is the intractable nature of the disease which prevents progress being as fast as we would wish.

Adequacy of M.R.C. Funds

Mr. BLENKINSOP asked if the Minister was satisfied with the amount of funds at present available for medical research; and what action he proposed to take to improve the situation. Mr. WALKER-SMITH: Yes, over the last ten years expenditure by the Medical Research Council has been more than trebled. The Council's resources are reviewed sympathetically each year in the light of new developments and new needs.

N.H.S. ADMINISTRATION

Senior Registrar Appointments

Mr. ROBINSON asked the Minister for a statement on the present position regarding time-expired senior registrars, indicating what proportion had been recommended for and have received permanent appointments. Mr. WALKER-SMITH: I explained my proposals in regard to time-expired senior registrars in my reply on April 21. Hospital boards have so far formulated proposals for 24 designated posts of which two are about to be approved and 22 are under consideration.

Mr. ROBINSON: Is that not a very small proportion of the whole? Why is progress so slow? Does the Minister not appreciate that a very great deal of anxiety and hardship is entailed? Mr. WALKER-SMITH: It has always been envisaged that there would be only a limited number of designated posts. I used that phrase, or words to that effect, in my answer on April 21. In regard to slow progress, it is a fact that two regional boards and five boards of governors have not yet replied, but I have reminded them of the urgency of doing so. Mr. A. BLENKINSOP: Does the Minister not feel that the time must come in a registrar's career when he needs some kind of certainty about his future? Mr. WALKER-SMITH: A good many of us in other fields of activity want certainty about our future (laughter)—on both sides of the House. We do our best for these people.

Hospital Waiting-lists

Mr. BLENKINSOP asked what was the latest available figure for those waiting for admission to hospital; and how this compared with twelve months previously. Mr. WALKER-SMITH stated that at the end of June, 1958, there were 442,000 names on the waiting-lists of N.H.S. hospitals in England and Wales. This figure was about 1% higher than that for June, 1957.

Mr. BLENKINSOP said there was great anxiety about the fact that during the last two years there had been a steady increase in the waiting-list compared with experience during some years before. What action was the Minister taking to secure a correction of this disquieting tendency? Mr. WALKER-SMITH: It has not been a steady increase. The figures fluctuate somewhat. At March 31 this year, for example, the figure was slightly lower than in March, 1957. In regard to previous years, the figures are a good deal lower than when Mr. Blenkinsop was concerned with these matters.

Medway Complaints

Mr. PERCY WELLS (Faversham, Lab.) asked the Minister if he had considered the complaints made at the annual general meeting of the Rochester and Chatham Division of the B.M.A. concerning the shortage of beds for acutely ill

patients in the Medway area. Mr. R. THOMPSON: I am aware of the need for more acute beds in this area, and the regional board is examining the possible use of the Royal Naval Hospital, Chatham, which will become available in 1961, to supplement the existing resources

Regional Board's Allocations

Mr. G. CHETWYND (Stockton-on-Tees, Lab.) asked for the additional allocations to each regional hospital board of the extra £1,750,000 for capital expenditure before March 31, 1959. The Minister supplied the following list of estimated sums from additional allocation to be devoted to capital works:

	£		£
Newcastle	105,000	Oxford	55,000
Leeds	121,000	South-western ..	140,000
Sheffield	138,000	Birmingham ..	66,000
East Anglia	30,000	Manchester	104,000
N.W. Metropolitan	125,000	Liverpool	107,000
N.E. Metropolitan ..	71,000	Wales	100,000
S.E. Metropolitan ..	110,000	Teaching hospitals	217,000
S.W. Metropolitan	225,000		

A note explains that the sum available for capital expenditure was part of a larger sum, and a measure of discretion was left to boards in dividing it between capital and revenue expenditure. The figures for capital are therefore not strictly comparable.

Form E.C.10A

Dr. DONALD JOHNSON asked the Minister whether he would sanction the use of Form E.C.10A by general practitioners in England and Wales to enable them to obtain supplies of dressings for emergency use in their surgeries. Mr. WALKER-SMITH replied that so far this had not proved practicable, but he would consider the matter further when he had the report of the Committee on the Cost of Prescribing. Dr. JOHNSON pointed out that the use of this form worked satisfactorily in Scotland. Mr. WALKER-SMITH explained that in Scotland it was a continuance of a scheme that was in force before the Health Service came into being, which was not the case in England.

Speech Therapists.—The Minister of Education is considering, in consultation with the Minister of Health, whether any special measures are necessary to meet the shortage of speech therapists.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

In Congregation on November 1 the degree of M.B. was conferred on J. C. Rice.

UNIVERSITY OF LONDON

The following candidates have been approved at the examination indicated:

THIRD M.B., B.S.—[1 2 3]E. R. Beck, [1 2 3 4 5]H. J. L. Francis (University Medal), [1 5]K. A. Harrison, [1 3 4]Eadie Heyderman, [1 5]K. J. Halley, [1 5]Valerie Little, [1 3 4]N. McIntyre, [1 2 3]Pauline S. Monro, [1 5]H. S. Platt, [1 4]E. B. Raftery, [1 3]D. J. Steward, B. C. S. Abbott, Mina A. Abou Shaqra, Elizabeth V. O. Agbettor, O. O. Akinkugbe, M. R. Aldous, A. R. Al Yusuf, A. C. Ames, I. F. Anderson, Mary E. Ashworth, T. W. Astin, M. A. Axelrad, Judith M. Babb, B. R. Baker, H. K. Baldwin-Price, J. R. Ball, F. Bannerman-Lloyd, D. H. Barham, D. F. Barrett, J. Barrie, D. C. J. Bassett, M. R. Baylis, B. K. Bayston, A. J. Bee, P. J. Bennett, W. H. Bevan-Thomas, Margaret A. Birchall, Patricia A. Blackwell, A. J. Blakeman, Sarah M. E. Blatch, J. Boyd, N. A. Boyd, J. F. Branton, P. R. Brass, P. P. Bricknell, C. R. Brown, N. E. Brown, M. Budd, L. J. Burton, M. F. H. Bush, W. P. K. Calwell, L. B. Cannell, I. R. Carr, P. A. Cartet, Suvendrini N. Casinader, M. I. D. Cawley, M. Charlesworth, R. K. Clarke, Diana Elizabeth Clough, W. J. B. Cocker, P. A. N. Colley, D. Connan, B. D. Cooper, T. A. Crantock, S. Craske, Jane M. Critchley, J. F. Cumming, B. C. Dando, G. R. Daniel, M. H. Darroch, Pauline M. H. Davidson, D. J. C. Davies, J. B. Davis, Margaret V. Dean, W. R. Dean, E. F. Doleman, A[l]son J. Dow, J. J. Elaife, D. J. Ellam, P. M. Ellis, R. W. Elsdon-Dew, E. R. Emmanuel, W. Erskine, J. A. F. Evans, P. J. Fenn, Davnet A. V. Fenton, J. M. Fowler, Frances E. Freeman, Ann F. Gamble, A. J. Gardner, Freda H. Garnett, P. M. Gelpke, P. N. Gillibrand, S. T. Godwin, M. J. Goggin, P. Gojaseni, A. Gooding, G. T. Gooding, J. Grant, J. P. Grier, Judith M. Hall, K. C. Hammond, C. C. E. Harbridge, P. B. Hardwick, G. Hass, A. A. Hawkins, R. T. Hawley, B. Hayes, A. F. Hayward, A. M. Hazell, Gillian C. Henly, A. B. Hewitt, Cynthia J. Heymeson, V. N. Highman, Joan M. Hinton, Juliet S. Hoare, O. Holmes, W. I. Hopkinson, E. J. Horgan, R. G. Hornung, Doreen M. Hudson, M. C. Hudson, F. D. Humphreys, H. Hunt, J. D. W. Hunter, J. Hyde, D. A. Hyslop, R. D. Illingworth, S. R. Jackson, R. W. James, D. G. Jenkins, A. D. S. Johnson, Rosemary A. Johnson, L. T. Jones, Mary O. Joseph, C. A. F. Joslin, Winifred N. Kaine, R. W. W. Kay, C. W. T. Keen, Mary B. Kelly, Delia M. Kenyon, C. J. Langridge, Patricia A. Last, J. M. Laurent, J. P. Lee-Potter, C. M. Liassides, M. M. Liberman, Marion R. Liss, C. O. Lister, W. R. Little, D. A. Logan, K. H. McCraith, Anthea McEwan, A. J. Macfarlane, D. C. MacNeill, A. Magrath, P. E. Mann, B. S. Mantell, M. S. Marston, L. J. Martin, F. B. Mayes, H. Meindok, J. L. Mercer, Yvonne M. Metcalf, P. V. Mills, A. J. E. Millwood, T. M. Moles, A. K. Monks, A. B. Morphy, G. Moses, D. F. Munro, W. Murdoch, M. Y. Najjar, Janet A. Napper, J. A. C. Neely, C. R. Necquaye, D. J. F. Nicol, A. I. Nwabueze, C. J. M. O'Keeffe, K. A. Olafimihan, Anne M. Olding, T. A. Oleghe, S. B. Oni, O. N. Onyeaso, A. A. Osindero, N. D. Parkin, M. C. Patterson, C. E. Perrin, J. G. Perry, P. O. D. Pharoah, Barbara Phillips, H. H. Phillips, R. M. Phillips, R. Pilkington, H. D. W. Plowright, D. I. Porter, D. Powell, D. J. Price, J. G. Pritchard, H. B. Raeburn, R. H. Raynes, A. P. Redmond, N. A. Rety, E. O. R. Reynolds, H. M. Richards, G. A. Richardson, J. M. R. Ridley, H. P. Rikard-Bell, J. F. Rivers, Janet R. Robbins, R. R. Roberts, R. G. R. Rosser, N. C. Russell, H. A. M. Samaan, Hildergard M. I. Seeman, C. A. Selway, Olive P. Sharp, Muriel A. Shiel, W. J. W. Siddall, N. A. Simmons, R. I. D. Simpson, B. R. T. Smith, Cynthia G. Smith, J. B. Sorapure, K. O. Sosan, Shirley H. Stanness, B. J. Stevenson, J. L. K. Tamakloe, J. G. Tetley, Veronica Thatcher, D. A. H. Thomas, Geraldine Thomas, R. A. Thompson, M. K. Tidman, N. Todd, J. B. Traherne, G. L. Tullett, P. Turner, M. J. Tynan, F. N. Udeh, J. G. Veszi, Ruth E. H. Wainwright, P. J. Ward, W. E. Waters, Ann E. R. Welch, T. P. Welch, Ann M. Willis, D. N. Wood, D. J. Woodgate, J. G. Wright, J. D. Young, I. I. Zayid.

[1]With honours. [2]Distinguished in pathology. [3]Distinguished in medicine. [4]Distinguished in applied pharmacology and therapeutics. [5]Distinguished in surgery. [6]Distinguished in obstetrics and gynaecology.

On October 22 the Senate awarded the degree of M.S. to L. B. Cohen.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on November 13, with the President, Sir James Paterson Ross, in the chair, D. A. Warrell (Portsmouth Grammar School) was admitted as Macloghlin Scholar.

A diploma of Fellowship in the Faculty of Anaesthetists was granted to Odile M. E. P. Plantevin.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

At a meeting of the Council of the College held on November 29, G. S. Mandal and A. K. Sarkar were admitted to the Membership of the College.

The following candidates were awarded the Diploma in Obstetrics:

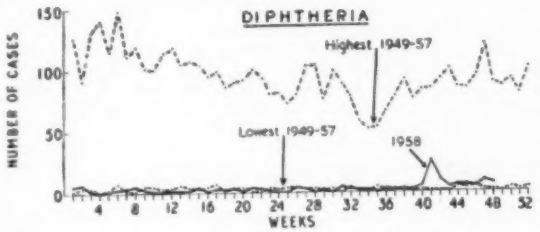
Margaret Aitken, Patricia M. Akers, Barbara A. Alcock, K. M. Allman, Joan Andrews, J. L. Andrews, H. T. Apsimon, A. E. Ashcroft, P. J. Ashton, W. M. Baggott, J. B. Ball, A. J. Barratt, Dorothy F. Bate, D. E. R. Bateman, M. A. Beale, G. Beaumont, W. A. Beck, P. G. Benson, G. H. Berry, J. F. Bird, A. Booth, Monica M. Brain, F. R. Braithwaite, E. W. Brentnall, J. F. Brooks, R. L. Buchanan, Patricia M. Bucknole, J. M. B. Burn, Eunice R. Burton, A. L. Bussey, Margaret A. Butler, L. R. Butler-Manuel, A. R. R. Cain, Pamela J. H. Callaghan, P. F. Cameron, Dorothy C. Campbell, W. Caplan, Kamla Chandiramani, K. Chapman, C. H. Chong, E. M. Clark, R. Clark, R. W. Clark, B. M. G. Clarke, Eleanor M. Clarke, J. C. Clarke, J. W. Clarke, A. D. Cole, J. A. Collie, R. A. Colwell, Johanna Connell, P. J. Constable, Anna Cope, J. D. Corcoran, G. Corney, D. G. Craig, J. L. Currie, J. deB. J. Dade, J. O. Dalrymple, T. P. Daly, R. J. Daniels, A. Darnborough, J. K. Dauncey, I. E. Daunt, G. A. Davenport, D. B. A. Ll. Davies, H. W. C. Davies, Pamela A. Deane, D. V. Dhupa, D. G. Dingle, Piyatissa Dissanyake, Cynthia M. Dixon, St. J. Dowling, P. M. Dunn, M. D. L. Eakin, A. M. Easty, R. W. Edmonds, Brenda A. P. Edwards, N. A. Elvin, Davina C. Embleton, S. Ende, G. L. Evans, R. R. Evans, D. K. Fairweather, G. W. M. Faris, J. H. N. Ferris, D. T. Finlay, Elizabeth C. Finn, G. Finnemore, F. L. P. Fouin, G. H. Fowler, A. H. Frame, M. J. N. Frohn, P. Garmon-Jones, J. N. Garrett, Susan George, W. H. S. George, J. H. Gervis, S. M. Gheewala, Jennifer M. D. Gibson, W. O. Goldthorp, Dulcie A. F. Goonewardena, R. L. Grant, R. D. Gray, R. I. Graymore, I. Gregg, Aloka Gupta, D. W. Hall, Ursula H. Hamilton, H. W. I. Hanan, Susan E. A. Hart, A. Haskell, T. D. Haskins, A. M. Hassim, M. J. Herlihy, F. Heyes, M. D. Hickman, N. A. Hiley, Jennifer Hill, Pamela M. Hogg, M. F. Holding, Aina J. Holt, J. Homi, Rachel S. Ll. Hood, C. V. Horn, P. Horsfield, B. L. Hoskyns, N. R. Houlston, J. K. Houston, B. G. Howarth, H. J. Hoyland, P. J. E. Hubbard, C. N. Hudson, D. I. Hughes-Davies, D. Hull, R. M. Humble, J. M. Hutchison, D. C. Hutfield, R. H. Huzzey, Christine M. Hyslop, N. M. Inamdar, G. A. Irving, Elizabeth J. Ives, P. N. Jarvis, Hilda Jayawardena, B. L. Johnson, D. S. Jones, Gwendolyn A. Jones, J. K. Ll. Jones, Margaret Jones, Anusuya Kalyanaraman, R. Keeley, J. C. Kennedy Smith, M. G. Kielty, N. D. Kilpatrick, H. A. P. King, R. G. P. King R. A. Lacey, R. D. Last, A. R. Lea, Shirley A. Leslie, J. W. Lewis, Patricia A. C. Locken, J. A. Lofting, B. E. Lomax, H. J. A. Longmore, J. Longstaff, Sheila Luthra, I. J. MacBean, I. G. Macdonald, G. J. R. McHardy, A. Macinnes, K. J. Mackay, Harriet B. MacKinnon, J. McMichael, D. P. Mason, Shanti Mathur, A. E. H. Mence, H. C. Meredith, W. K. Merifield, M. D. Middleton, J. K. Mills, Frances F. Milne, J. A. Mitchell, R. J. R. Moffat, Ann H. Montford, T. Morley, D. C. Morrell, P. Morris, J. Morrison, K. F. C. Muncey, Mary C. Munday, Aileen C. Munro, D. S. Munro, P. J. S. Murray, Pamela M. Mylward, B. R. Neill, E. M. Newton, Nora M. Norris, T. D. Nundy, A. F. O'Grady, O. A. Ojo, D. J. O'Shaughnessy, Jean B. Owens, S. K. Panja, M. E. Parry, D. G. Paskin, R. I. Patel, W. G. Paterson, R. S. Peachey, J. F. Perren, G. D. Phillips, G. Phillips, Hazel M. Phillips, S. G. Phillips, A. J. Platts, M. R. K. Plaxton, Ann M. Pocock, C. R. Porteous, G. Priddle, Saroja Ramaswamy, Dorothy E. Robb, I. Roberts, N. G. Roberts, Shirley B. Robertson, J. N. Rodrigo, P. S. Rolland, I. G. Ross, A. R. Roy, J. A. Rumbie, J. G. B. Russell,

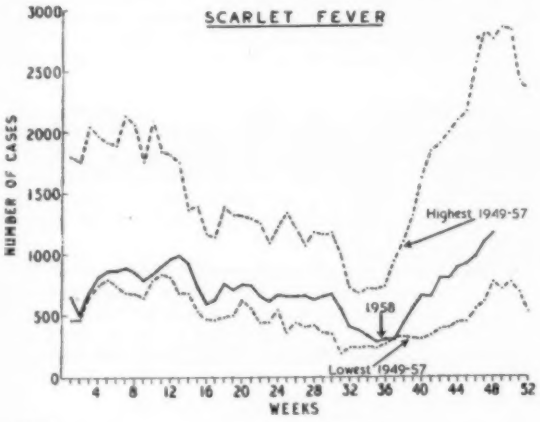
N. E. Rust, S. Sarin, H. Savery, P. Savithri, J. V. Sawdy, J. B. Sayer, T. D. Sayer, Maria Schaffner, S. C. C. Scott, R. J. Sellick, A. Abu-el-Futuh Shandall, N. W. Shephard, M. A. Shields, M. Shillito, Y. Shirazi, M. W. Sleight, W. D. Smith, Shirley M. Snead, K. G. R. Somer, D. M. Sopher, S. P. Spiers, J. H. Stewart, J. Strahan, E. W. Sturton, S. K. Suppal, D. A. Swales, N. D. V. Swallow, S. G. Taylor, J. G. Tees, Pamela M. Thorne, T. M. Tibbetts, W. S. H. Tow, A. S. Townsend, L. Tragan, R. F. Tuckett, Paruvangada M. Uthappa, J. A. M. Vasey, J. F. Walker, Margaret M. Walshe, K. H. Warden, Judith C. R. Wardle, R. S. Wardle, R. W. Ware, A. R. Warner, C. G. Waters, A. N. Watson, Gillian A. Watson, D. A. L. Watt, I. Watts, P. Wellings, H. J. O. White, D. H. Williams, P. Wolstencroft, C. D. Wooding, S. J. P. Woods, T. K. W. Woolacott, P. N. Wormald, A. J. Zuckerman.

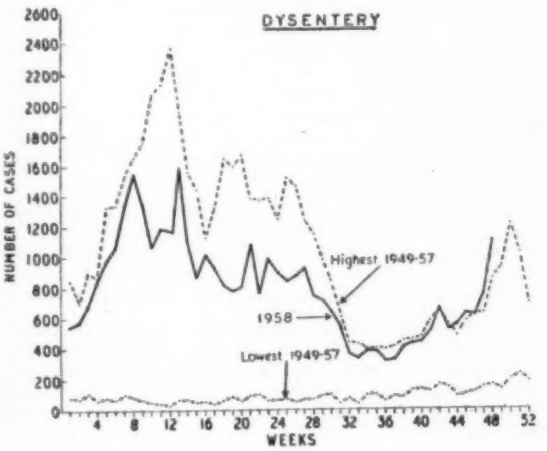
Vital Statistics

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus - - - - - -, the figures for 1958 thus ————. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **November 29** (No. 48) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria ..	7	2	8	0	2	5	2	1	0	3
Dysentery ..	1,098	95	166	20	1	461	94	131	14	
Encephalitis, acute	4	0		0		2	1		1	
Enteric fever:										
Typhoid ..	3	2	0	0	1	2	1	0	0	2
Paratyphoid ..	5	1	3(B)	0		5	0	0	0	
Food-poisoning ..	236	17	9	1	1	151	22	8	1	
Infective enteritis or diarrhoea under 2 years				16	27				6	19
Measles*	6,910	398	190	32	365	1,843	37	28	32	20
Meningococcal infection	16	0	14	1		22	0	8	0	1
Ophthalmia neonatorum	26	8	7	0		36	2	8	0	
Pneumonia† ..	407	40	197	8		486	36	325	7	38
Poliomyelitis, acute:										
Paralytic ..	50	1	3	1	6	39	2	6	2	3
Non-paralytic ..	19	0				17	1			
Puerperal fever§ ..	184	23	11	0		208	40	15	2	
Scarlet fever ..	1,164	82	127	23	48	772	64	64	13	15
Tuberculosis:										
Respiratory ..	480	45	116	15		595	74	104	25	
Non-respiratory	65	14	10	4		64	2	14	1	
Whooping-cough	724	29	78	90	106	635	27	56	1	32

DEATHS	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria ..	0	0	0	0	0	No comparable figures available.	0	0	0	0
Dysentery ..	0	0		0			0		0	
Encephalitis, acute		0			0		0			1
Enteric fever ..	0	0	0	0			0	0	0	
Infective enteritis or diarrhoea under 2 years	7	0	0	0	1		0	1	0	2
Influenza	11	0	2	2	1		14	6	1	13
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	2				0	0		
Pneumonia ..	533	42	19		10		54	28	12	9
Poliomyelitis, acute	8	0		0	0		1		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	111	8	8	0	5		19	8	2	5
Non-respiratory		1	0	0	0		0	0	0	0
Whooping-cough	1	0	0	0	0		0	0	0	0
Deaths 0–1 year ..	327	27	27	4	10		27	38	5	14
Deaths (excluding stillbirths) ..	10,403	859	532	129	149		939	709	125	185
LIVE BIRTHS ..	13,396	1167	1013	197	307		1101	955	205	387
STILLBIRTHS ..	327	33	22				22	22		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Chair of Medicine, St. George's Hospital.—Dr. A. C. DORNHORST, reader in medicine at St. Thomas's Hospital Medical School, has been appointed to a new London University chair of medicine at St. George's Hospital Medical School. Dr. Dornhorst graduated in medicine from St. Thomas's in 1937, proceeding M.D.(London) in 1939. He obtained the M.R.C.P. in 1938 and was elected F.R.C.P. in 1955. During the second world war he held the rank of lieutenant-colonel in the R.A.M.C.

Carbon-monoxide Poisoning.—In a circular to local authorities, dated December 8, the Ministry of Health amends the scale of medical and first-aid equipment in the Ambulance Service to bring it into line with the Medical Research Council's recent recommendations on the treatment of carbon-monoxide poisoning (*Journal*, December 6, p. 1408). The circular states that the Minister "has been advised by the Medical Research Council that, for the purpose of first-aid treatment of carbon-monoxide poisoning, use should be made of 5% carbon dioxide in oxygen instead of pure oxygen. He is further advised that pure oxygen should be used in the treatment of asphyxia and anoxia."

Research on Mental Deficiency.—On December 16 a new diagnostic and research department was opened at the Fountain Hospital, Tooting Grove. Space for the department has been found by adapting and redesigning what was previously a ward and adding a biochemical laboratory to it. The unit includes a day room for the children and two small dormitories (for 8 and 4 beds). Research into the cause and treatment of mental deficiency has been actively developed at the Fountain Hospital under Dr. BRIAN H. KIRMAN, and the new unit will make it possible with less disturbance to investigate and treat selected groups of children. At present two groups of children are in the unit, one for a biochemical investigation of phenylketonuria and the other for trial of a pituitary treatment of mongolism.

Handicapped School-leavers.—The British Council for Rehabilitation has set up a Working Party under the chairmanship of Dr. ELFED THOMAS, director of education for the City of Leicester, with the following terms of reference: "To investigate the needs of the physically and mentally handicapped school-leavers; to study the means of meeting their difficulties and to make recommendations." The Working Party includes educationists; representatives of the medical services, voluntary organizations, the Trades Union Congress, and industry, and observers from Ministries and local authorities. The British Council for Rehabilitation (Tavistock House South, Tavistock Square, London, W.C.1) would welcome evidence relevant to the above terms of reference.

Ciba Fellowship Trust.—Ciba Clayton Ltd., Ciba Laboratories Ltd., Ciba (A.R.L.) Ltd., and the Clayton Aniline Company Ltd. announce that they have set up a Ciba Fellowship Trust "for the purpose of improving and increasing the interchange of ideas between scientists in the United Kingdom and on the Continent. The trustees are Sir ARTHUR HARVEY, M.P., Lord HIVES, C.H., and Sir ALEXANDER TODD, F.R.S.

Several fellowships will be awarded for tenure during the academic year 1959–60 at Continental universities or for research in chemistry, physics or allied subjects. They will be awarded to graduates of United Kingdom universities or those who graduate there. Basic awards will vary between £500 and £800 a year.

Further details may be obtained from the secretary of the Trust, Ciba (A.R.L.) Limited, Duxford, Cambridge. The closing date for applications is January 31.

Royal Society.—Among those elected at the anniversary meeting of the Royal Society on December 1 as office holders for 1959 were Sir LINDOR BROWN as biological secretary; and Sir CHARLES DODDS, Professor WILSON SMITH, and Professor J. Z. YOUNG as members of the council. Under the Royal Society and Nuffield Foundation Commonwealth bursaries scheme awards have been made to Dr. P. R. DAVIS (Royal Free School of Medicine) and Dr. A. IGGO (Department of Physiology, Edinburgh University). The former is to study primate skeletal remains in Africa, the latter neurophysiological techniques at Canberra.

Royal College of Physicians of Edinburgh.—The office bearers for the ensuing year are: *President*, Dr. A. RAE GILCHRIST; *vice-president*, Dr. J. D. S. CAMERON; *members of council*, Dr. I. G. W. HILL, Dr. J. G. M. HAMILTON, Dr. J. HALLIDAY CROOM, Dr. T. ANDERSON, and Dr. J. LAURIE; *treasurer*, Dr. J. ALASTAIR BRUCE; *secretary and registrar*, Dr. R. F. ROBERTSON; and *hon. librarian*, Dr. JOHN RITCHIE.

Royal College of Surgeons of Edinburgh.—At a meeting of the College on December 10, with Professor JOHN BRUCE, the president, in the chair, the fellowship without examination was awarded to Professor G. J. ROMANES. At a meeting held the same day the following who passed the requisite examinations were admitted fellows:

B. C. Abernethy, R. T. Aldridge, B. Azer-Fam, G. W. Burgess, I. Cher, A. B. Chinnappa, T. B. Comins, K. S. Davies, K. J. Dennis, A. K. Deshmukh, M. J. Flood, R. L. Gadd, D. S. Gill, A. G. Graham, J. M. Gray, H. Green, W. A. Hanna, J. A. Hunt, V. C. James, K. M. Kalappa, D. M. King, P. A. H. Knocker, S. G. Leitch, D. B. Longmore, C. R. Lulham, D. H. McClymont, A. E. Mody, P. J. B. Murray, J. R. Pearson, W. S. E. Perera, I. H. Rathor, M. R. Rayman, C. J. C. Renton, F. O. Stephens, R. D. Stride, N. Swarup, K. P. Tamaskar, H. J. S. Waldeck, G. F. Walker, R. K. Wats, and R. W. Weinberg.

Royal Faculty.—At a meeting of the Royal Faculty of Physicians and Surgeons of Glasgow on December 1, with Mr. ARTHUR JACOBS, the president, in the chair, the following were admitted fellows, *qua* physician: P. Damodaram, T. D. Grant, I. R. W. Lominski, A. MacNiven, I. Ramzy, M. A. Shoke.

Sheffield University.—A special degree congregation will be held on the occasion of the opening of the New University Library by Mr. T. S. ELIOT, O.M., on May 12, at which the honorary LL.D. will be conferred on Professor ROBERT PLATT, P.R.C.P., and the honorary D.Sc. on Sir HANS KREBS, F.R.S., Whitley professor of biochemistry at Oxford.

Empire Rheumatism Council.—Dr. J. THOMAS has been awarded a research fellowship for work on connective tissue enzymes. The Geigy travelling fellowship has been awarded to Dr. EVELYN HESS, who will spend a year at the Texas Southwestern Medical School, and the Wyeth fellowship in pharmacology has been awarded to Dr. V. MOSES for work on salicylates and other antirheumatic drugs.

British Association of Plastic Surgeons.—The following have been appointed to office for 1959: *President*, Mr. RAINSFORD MOWLEM; *immediate past president*, Mr. J. S. TOUGH; *hon. treasurer*, Mr. R. P. OSBORNE; *hon. editor*, Mr. A. B. WALLACE; *members of council*, Mr. T. GIBSON, Mr. P. H. JAYES, Professor T. P. KILNER, Air Commodore G. H. MORLEY, Mr. E. W. PEET, Mr. MORTIMER SHAW, and Dr. STUART GORDON (overseas representative); and *hon. secretary*, Mr. C. R. MCLAUGHLIN.

British Association of Otolaryngologists.—The following have been elected officers for 1958–9: *President*, Mr. C. GILL-CAREY; *immediate past president*, Mr. I. SIMSON HALL; *vice-president*, Mr. R. R. SIMPSON; *hon. treasurer*, Mr. J. C. HOGG; and *hon. secretary*, Mr. MYLES L. FORMBY.

Christine Murrell Fellowship.—The Medical Women's Federation invites applications for this research fellowship, value £150, from Women on the British *Medical Register*. Further details from the Federation, Tavistock House North, Tavistock Square, London, W.C.1. The closing date is April 30, 1959.

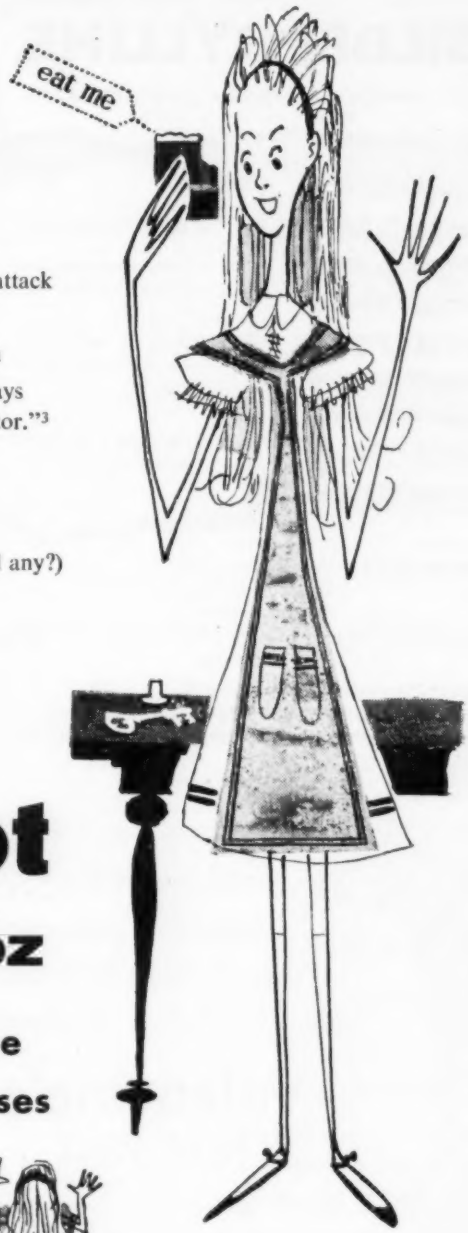
Migraine in Wonderland

The fantasies of altered body size and shape in *Alice in Wonderland* are like those experienced by some migraine patients.[1] Disorders of body image may be found in migraine either as an aura to an attack or as a migrainous equivalent.[2]

Lewis Carroll himself suffered from migraine,[1] and it may well be that "Alice trod the paths and byways of a Wonderland well known to her creator."[3] If that is so, English literature is the richer for Mr. Carroll's migraine.[2]

Curiouser and curiouser... to picture Alice's adventures (would she have had any?) if Cafergot had been at hand for Lewis Carroll's migraine...

[1] *J. nerv. ment. Dis.* (1952) **116**, 346 [2] *Lancet* (1956) **I**, 794
[3] *Canad. med. Ass. J.* (1955) **73**, 701



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Deputy Chief Nursing Officer.—The MINISTER OF HEALTH has appointed Miss DOROTHY MARION WHITE to be Deputy Chief Nursing Officer. From 1955 to 1957, Miss White was assistant matron at the General Infirmary, Leeds. Since then she has been assistant nursing officer to the S.E. Metropolitan Regional Hospital Board.

COMING EVENTS

Joint Endocrine Meeting.—The Section of Endocrinology of the Royal Society of Medicine and the Society of Endocrinology, with other interested bodies, are holding a joint meeting on April 24 and 25 at the Royal Society of Medicine. Details from the Section Secretary of the R.S.M., 1, Wimpole Street, London, W.1.

1959 Health Education Conference.—The conference will be on "The Elderly in the Community," January 22, 1959, at B.M.A. House (fee £1). Details from the Medical Director, Central Council for Health Education, Tavistock House North, Tavistock Square, London, W.C.1.

National Association for Mental Health.—Residential week-end conference in London for A.M.O.H.s working in maternity and child welfare clinics, February 20 to 22, 1959. Applications (by January 12, 1959) to the Education Secretary, N.A.M.H., 39, Queen Anne Street, London, W.1.

Ninth International Congress of Paediatrics.—The Congress will be held in Montreal from July 19 to 25. Application forms from the Hon. Secretary, British Paediatric Association, c/o Institute of Child Health, Great Ormond Street, London, W.C.1.

Darwinism and the Study of Society.—Conference to mark the centenary of *The Origin of Species*. April 8 to 10, 1959, at Adam House, Edinburgh. Details from Dr. M. P. BANTON, Social Sciences Research Centre (Edinburgh University), 39, George Square, Edinburgh, 8.

Ophthalmological Society of the U.K.—Annual congress, April 9 to 11, 1959, at the Royal Society of Medicine. Details from the Ophthalmological Society, 47, Lincoln's Inn Fields, London, W.C.2.

Medical Education and Licensure.—55th A.M.A. annual congress on medical education and licensure, Chicago, February 7 to 10, 1959. Details from the Council on Medical Education and Hospitals, American Medical Association, 535, North Dearborn Street, Chicago, 10, Illinois.

British Association of Physical Medicine.—Annual meeting, April 17 and 18, 1959, at Guy's Hospital. Last date for papers, January 30, 1959. Details from the B.A.P.M., 47, Lincoln's Inn Fields, London, W.C.2.

Central Council for Health Education.—Seminar in London for M.O.H.s on "The Promotion of Health in Middle Age," February 24 to 27, 1959. Details from the Medical Director of the Council, Tavistock House North, Tavistock Square, London, W.C.1.

International Congress on Plastic Surgery.—The British Association of Plastic Surgeons is holding an international congress in London from July 12 to 17, 1959. Detailed information may be obtained from the Organizing Secretary, Mr. DAVID MATTHEWS, International Congress on Plastic Surgery, c/o Institute of Child Health, Hospital for Sick Children, Great Ormond Street, London, W.C.1.

Pneumoconiosis.—The pneumoconiosis conference of the South African Council for Scientific and Industrial Research will be held from February 9 to 24, 1959, in Johannesburg. Details from the Secretary-General, 18, London House, Loveday Street, Johannesburg.

Institute of Diseases of the Chest.—Clinical demonstrations (without fee) for medical practitioners, on Fridays at 5 p.m. from January 2 to March 20, 1959. Details from the Secretary of the Institute, Brompton, London, S.W.3.

James Yearsley Lecture.—Dr. KARSTEN KETTEL, of Hillerod, Denmark, will lecture at 5.15 p.m. on March 6, 1959, at the Royal Society of Medicine, on "Surgery of the Facial Nerve in Atraumatic Facial Palsies."

APPOINTMENTS

ASH, E. BAYLIS, M.B., M.R.C.P., Honorary Consulting Dermatologist, United Birmingham Hospitals.

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—P. E. Jackson, M.D., M.R.C.P., Consultant Physician, Peterborough and Stamford Hospital Group); J. W. Dickson, M.B., B.S., F.R.C.S., Consultant Orthopaedic Surgeon, Ipswich and East Suffolk Hospital Group; A. Bryce, M.B., Ch.B., D.M.R.D., Consultant Radiologist, North Cambridgeshire Hospital Group; F. L. F. Innes, M.B., Ch.B., F.R.C.S.Ed., Consultant Plastic Surgeon, Regional Burns and Plastic Unit, West Norwich Hospital; J. Zamler, M.B., B.S., Assistant Clinical Pathologist, Papworth Hospital and County Hospital, Huntingdon; J. A. Morgan-Hughes, M.B., B.Chir., Medical Registrar, Norfolk and Norwich Hospital; M. C. G. Mantell, M.B., B.Chir., Anaesthetic Registrar, United Norwich Hospitals; B. S. Kumar, M.B., B.S., Surgical Registrar, Memorial Hospital, Peterborough; J. W. Smith, M.B., B.S., Surgical Registrar, West Norfolk and King's Lynn General Hospital; T. Osborn, B.M., B.Ch., Registrar in Psychiatry, Fulbourn Hospital and Addenbrooke's Hospital.

ELLIOTT, FRANK A., M.B., Ch.B., F.R.C.P., Professor of Clinical Neurology in the Medical School of the University of Pennsylvania, and Director of Neurological Research and Education at the Pennsylvania Hospital, Philadelphia.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—M. A. T. Waters, M.B., B.S., M.R.C.P.Ed., D.P.M., Consultant Psychiatrist at Roundway Hospital, Devizes; D. R. Talwar, M.B., B.S., D.A., Anaesthetic Registrar at Southmead Hospital, Bristol; A. J. Newton, M.B., B.S., Registrar in Orthopaedic and Traumatic Surgery to work at Torbay Hospital, Torquay, and Princess Elizabeth Orthopaedic Hospital, Exeter, on an exchange basis; F. W. Ward, M.B., B.S., Surgical Registrar at Cheltenham General Hospital.

WYLIE, J. A. H., M.D., D.Phil., Research Bacteriologist, Department of Bacteriology, Brompton Hospital.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Aikman.—On December 5, 1958, at his home, 72, Chelmsford Place, Fulford Road, York, James Hislop Aikman, *M.C.*, M.B., Ch.B., D.P.H.

Beatty.—On November 26, 1958, at Tunbridge Wells, Kent, John Colley Pounden Beatty, M.B., B.Ch., D.P.H.

Blair.—On December 7, 1958, at Bridge Street, Helmsley, Yorks, Alexander Campbell Blair, M.D., aged 90.

Boyden.—On December 5, 1958, Percy Hamilton Boyden, M.D., surgeon captain, R.N., retired, of 30, Outram Road, Southsea, Hants.

Bryson.—On November 30, 1958, at Richmond, Surrey, Reginald Bryson, F.R.C.S.Ed., Lieutenant-Colonel, I.M.S. (retired), aged 86.

Burrell.—On December 7, 1958, at Aberystwyth, Cards, Charles Milwyn Burrell, M.B., B.Ch., of 22, North Parade, Aberystwyth.

Cardis.—On December 1, 1958, at 32, Street Lane, Leeds, Yorks, Joseph Cardis, M.D., aged 57.

Clyne.—On November 29, 1958, at Wealdens, Ashurst, near Southampton, Hants, Charles Clyne, *M.C.*, M.D., D.T.M.&H.

Cremin.—On December 3, 1958, in hospital, Maurice Cremin, L.R.C.P.& S.I. & L.M., of 40, Heather Drive, Dartford, Kent.

Curtiss.—On December 11, 1958, Edgar Stuart Curtiss, T.D., M.B., B.S., F.F.A. R.C.S., of Beaconsfield, Bucks, and Ealing, London, W.

Devitt.—On December 8, 1958, at Bournemouth, Hants, Herbert Pye Smith Devitt, M.R.C.S., L.R.C.P.

Lamb.—On December 9, 1958, in a nursing-home, Teddington, Middx, David Lamb, M.B., C.M., F.R.F.P.S., J.P., late of 70, Mount Annan Drive, Glasgow, aged 88.

Lambkin.—On December 4, 1958, Ernest Charles Lambkin, D.S.O., M.B., B.Ch., Lieutenant-Colonel, R.A.M.C. (retired), of Liskilleen, Shankill, Co. Dublin.

Mecredy.—On December 4, 1958, Emily Mary Spencer Mecredy, M.D., of 11, Devonshire Place, London, W., formerly of 148, Harley Street, London, W.

Neill.—On December 1, 1958, at Northern General Hospital, Edinburgh, James Hood Neill, M.B., Ch.B., of 4, Blinkbonny Crescent, Edinburgh, formerly of Kenya and Uganda.

O'Brien.—On December 7, 1958, William O'Brien, M.B., Ch.B., of 284, Brockley Road, London, S.E.

O'Connor.—On November 23, 1958, at his home, Ashwood House, Swindon Road, Kingswinford, Staffs, William Albert O'Connor, L.M.S.S.A., D.P.M., aged 61.

Philip.—On December 7, 1958, at Balbogie, Huntly, Aberdeenshire, Peter William Philip, M.B., Ch.B., J.P.

Phillips.—On December 10, 1958, at 7, Kilgraston Road, Edinburgh, Joseph Evelyn Phillips, M.B., Ch.B., of Barbados, British West Indies, late of 49, Minto Street, Edinburgh.

Rowlands.—On November 22, 1958, at 25, Wimpole Street, London, W., Richard Pugh Rowlands, M.R.C.S., L.R.C.P., aged 86.

Smith.—On November 28, 1958, at Putney, London, S.W., Hoyland Smith, M.R.C.S., L.R.C.P.

Southwell-Sander.—On December 6, 1958, at his home, 8, Old Bury Hill, Dorking, Surrey, Geoffrey Henry George Southwell-Sander, M.B., B.Chir., D.P.H., D.I.H., Surgeon Captain, R.N.

Stansfield.—On November 18, 1958, in hospital at Stroud, Walter Stansfield, M.R.C.S., L.R.C.P.

Taylor.—On December 6, 1958, Elizabeth Morton Taylor, L.R.C.P.&S.Ed., L.R.F.P.S., of Ormisbank, Dalkeith, Midlothian, aged 88.

Wall.—On November 25, 1958, at Paignton, Devon, Austin Darley Wall, M.B., F.R.C.S.

Watts.—On December 3, 1958, Edward Croft Watts, M.D., F.R.C.S.Ed., D.P.H., of Lothians, Milford-on-Sea, Hants, aged 86.

Weatherhead.—On November 22, 1958, at a Folkestone nursing-home, Ernest Weatherhead, M.B., of 1, Grimston Gardens, Folkestone, Kent, aged 84.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Surgery for Diaphragmatic Eventration

Q.—*Has surgery anything to offer in the treatment of diaphragmatic eventration in a patient of 64, whose symptoms are now becoming distressing on account of very considerable cardiac displacement to the right—the eventration being of the left leaf of the diaphragm?*

A.—I assume that the patient has true eventration, a congenital defect in which the central tendon of the diaphragm is thinned and elevated but the muscle itself is intact and functional. The condition does not usually give rise to any ill effects but may cause gastric or cardio-respiratory symptoms. It may increase disability in an emphysematous patient with depressed pulmonary ventilation and vital capacity, not only by diminishing the total lung volume but also by allowing paroxysmal diaphragmatic movement. A thorough investigation of the cardio-respiratory system is essential in a patient of this age to ensure that the symptoms are not primarily cardiac in origin (it is unlikely that displacement of the heart *per se* will give rise to disability). Before any operation is contemplated all other means should be taken to increase pulmonary efficiency. If respiratory function is embarrassed by obesity, vigorous dieting is necessary. The patient should be advised to stop smoking. If, after all else has failed, there is good reason to suppose that pulmonary function would be significantly improved by restoring the diaphragm to its normal situation, then operation should be considered. However, this is a relatively recent development in thoracic surgery, and the results of treatment are not fully known.

Post-operative Bleeding in Hereditary Pseudohaemophilia

Q.—*What is the treatment of post-operative bleeding associated with von Willebrand's disease (hereditary pseudohaemophilia)? Nillson et al.[1] suggest that a blood protein fraction is a specific. If injected at the time, it stops bleeding, or it can be given pre-operatively in known cases. Is this correct? Is the substance available in England; what is the dose; is it safe; and can it be used as a diagnostic test?*

A.—The main haemostatic defect in von Willebrand's disease is a constitutional capillary abnormality. Coagulation defects may accompany the disease, but are, from the practical point of view, less important. When such a patient undergoes operation profuse bleeding from capillary vessels is the rule. If this bleeding is immediately arrested by firm pressure until clotting has occurred subsequent bleeding is not usually troublesome. But of course not all sites are susceptible to the application of firm pressure for five minutes. Thus a material which temporarily controlled the capillary bleeding would be a great advantage. The report of Nillson referred to is most promising and there is no reason to doubt the author's results. A similar, but not identical, material is made in this country by the Lister Institute. It has, so far as I know, not yet been used to control bleeding in patients with von Willebrand's disease and there is no guarantee that the material would have the effect described by Nillson. Moreover, there is no certainty that all patients classified as having Willebrand's disease have exactly the same defect. Again, the material, being prepared from fresh plasma, is in very short supply. Thus the questions of possible dosage, safety, and use as diagnostic material must await future research.

REFERENCE

[1] Nillson, I. M., Blombäck, M., Jorpes, E., Blombäck, B., and Johansson, S. A., *Acta med. scand.*, 1957, **159**, 179.

Treatment for Petit Mal

Q.—*What treatment can be given to a child of 3 years who has petit mal and who has not responded to phenobarbitone or to "mysoline" and "diamox"?*

A.—A most useful drug in petit mal is "tridione" (troxidone). To a child of 3 it can be given as a tablet of 0.15 g., or as tridione solution, each drachm of which contains 0.15 g. An average dose would be 0.15 g. four times a day. If tridione does not control the attacks, "paradione" (paramethadione) is worth trying. This is made up as pills, each containing 0.3 g., or as a solution, 1 ml. of which contains 0.3 g. The dosage is the same as tridione. The danger of these drugs, particularly of tridione, is agranulocytosis. Accordingly total and differential white counts should be performed when patients are on these drugs.

Aetiology of Pyloric Stenosis

Q.—*Is pyloric stenosis less common in babies fed "on demand" than in those fed at fixed intervals?*

A.—Congenital hypertrophic pyloric stenosis diagnosed by palpating the tumour and confirmed by radiography or by demonstration of its presence at operation is a familial condition. Furthermore, the tumour itself may be present at birth. It has recently been described in one of conjoined twins. It seems likely, therefore, that the basic cause is genetic, and possibly no other factor is involved. It has, however, at times been suggested that a second factor is required to produce the muscular hypertrophy and that this might be connected with overfeeding or with some other form of feeding mismanagement. There is no real evidence for this. Neither is there any statistical evidence to show whether or not pyloric stenosis is less common in demand-fed babies than others, but it seems unlikely. "Pyloric stenosis" is sometimes diagnosed on less strict criteria, with the result that other causes of vomiting are labelled as "pyloric stenosis," and it is possible that claims for an emotional or functional origin of the muscle hypertrophy have been based on such cases.

Dermatitis in Dentists

Q.—*What are the common causes of dermatitis of the tips of the fingers in a dentist?*

A.—The commonest cause is allergic sensitiveness to contact with local anaesthetics, but all other contacts in dentistry should be considered, such as antiseptics, antibiotics, nickel, chrome, oil of cloves, amalgam, acrylic resin, etc. In a recent case of this type the problem was not solved until patch-tests had extended to the home field and incriminated a streptocarpus plant.

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